Difficult Diagnosis

A GUIDE TO THE INTERPRETATION OF OBSCURE ILLNESS

By

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THIS VOLUME IS GRATEFULLY DEDICATED
TO MY DEVOTED WIFE

CAROL ANTONIA ROBERTS

*whose patience and encouragement were indis-
pensable in bringing its concept to a reality*

PREFACE

THIS WORK is presented with the hope that it will prove a worthwhile supplement to the numerous other volumes and journals which the reader utilizes in his own analysis of difficult diagnostic problems Its sole claim to uniqueness rests in the facts that it has been prepared by a single practicing internist and that it sets forth those diagnostic considerations which he believes should be readily available to the consultant clinician The orientation of the book is explained in greater detail in the Introduction

I am certain of one reason why I undertook the writing I needed a book like this in my own practice The tasks of culling evaluating collating and writing have been so educative as to have already repaid me for my efforts I hope that the finished volume may serve, for others, as a substrate onto which can be grafted additional gleanings from our enormous literature

There can be little doubt that this effort will be challenged by many 'practical' clinicians on the grounds that it deals with too many "rare birds" or, put in another way, that neither they nor the author could possibly encounter some of the disorders described herein more than once or twice in a lifetime On the other hand it is my conviction that "revelation comes only to the prepared mind," and that both the unusual diseases for which a specific treatment is (or might become) available and the uncommon manifestations of common disorders should hold important positions in the thinking of those who would pride themselves upon being diagnosticians

"*Was man weiss man sieht*"
(What one knows one sees)
GOETHE

H J ROBERTS

ACKNOWLEDGMENTS

HOWEVER LONG and diligently an author may labor in preparing a work—particularly one designed to serve as a useful reference text by experienced and discriminating colleagues—the successful fruition of such an effort is mediated by the added talents of others This treatise is no exception

I should like to express my gratitude to the following esteemed friends and teachers who have reviewed the manuscript in part and have given valuable comments Dr Ralph Myerson Dr Jacob Weber, Dr Lewis Hurxthall, Dr Victor McKusick, Dr Mark Lepper, and Dr Walter Shelley

To Esther Roberts Constance L Marcoux, Lauretta Masterson Jeannette Smith, Roberta Merrette, and Frieda Neumann, I am obliged for tedious secretarial services Miss Ruth L Menninger, Mrs Christine Landram and Mrs Anna Rymer have rendered valuable help with the bibliography

The assistance and guidance of the W B Saunders Company were truly indispensable Only one who has already gone through the process of having his first book published can begin to appreciate the value of the counsel the experience, and above all the patience and encouragement of the publisher in overcoming the countless editorial and typographical problems that beset an author The Saunders editorial staff has offered an extraordinarily high caliber of aid, starting from the processing of the original manuscript

I cannot conclude this theme of thanks without expressing my deep appreciation to the multitude of physician authors cited in the bibliographies whose experiences have so enriched my comprehension of medicine through their sincere literary efforts

H J ROBERTS

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Introduction

"Satius est initius mederi quam fini"
(It is better to doctor at the beginning than at the end)
ERASMUS

"He will manage the cure best who has foreseen what is to happen from the present state of matters
HIPPOCRATES

IN AN ERA which abounds in the mass of medical texts and literature that is characteristic of ours I have been asked what the indications for another volume on medical diagnosis might be (and particularly so in view of its basic ' organic orientation) Accordingly I am taking the author's prerogative in this introduction to set forth those considerations which not only prompted me to attempt such a treatise, but which also served as guides in choosing and assembling its present content and form

This book will present the system of a practising internist that has served him well as a valuable and practical Ariadne s guiding thread through the diagnostic labyrinth of obscure illness It is not set forth as a "primer ' in diagnostics even though the author has made every effort to make the text as readable as possible Rather, its orientation is on an advanced postgraduate level for clinicians whose experience and skepticism will critically dictate to them its place in the analysis of difficult case material Conversely for one who is not thoroughly grounded in the disciplines of everyday diagnostics, it is cautioned that there are many potential pitfalls in this type of medical reading

I am keenly and humbly cognizant of the many omissions and commissions the very nature of this book necessitates A similar feeling relates to the limitations of knowledge which arise when a single physician attempts such a comprehensive volume in this age of multiple authorships In the final analysis the present effort stemmed largely from an admonition similar to that expressed by Hobbes of the importance "for any man that aspires to true knowledge to examine the definitions of former authors, and either to correct them when they are negligently set down, or make them for himself

In the course of the practice of medicine, every physician and consultant encounters problem patients who, after careful history and exam

ination, appear to be suffering from persistent symptoms of both a general nature and from those referable to several specific systems of the body The *routine* laboratory and x ray diagnostic procedures may be either "negative," "borderline," or "inconclusive" He is then faced with the problem of (1) biding his time, hoping that subsequent events in the clinical course may clarify the nature of the patient's condition, (2) diagnosing the symptom complex as psychosomatic, if significant elements of anxiety or depression are present, or (3) intensively pursuing further diagnostic approaches in the hope that a specific treatment or prognosis may be more readily ascertained It has repeatedly impressed the author that these difficult diagnostic problems are definitely on the increase in this transitional age of medicine, characterized as it is by both the continuing effective control of acute illness and the undeniable emphasis upon disease affecting the middle and older age groups

In a sobering analysis of the diagnostic errors encountered during a recent study of 1106 autopsies at one center Gruver and Freis observed that the correctable misdiagnoses could be attributed as frequently to deficiencies involving medical judgment alertness, and thoroughness as to the actual lack of medical knowledge In the main they found these shortcomings to include the following (1) the failure to obtain routine screening tests, particularly roentgenograms of the chest, (2) the ignoring of positive symptoms, signs or laboratory reports which did not fit in with the initial diagnostic impression, (3) the failure to repeat pertinent laboratory tests, (4) attributing the patient's present illness entirely to complications of a previously diagnosed disease state (5) the false sense of security engendered by misleading negative laboratory reports, particularly x ray films which initially did not disclose the lesion, and (6) in long illnesses, the failure to review and summarize the accumulated data, and to repeat the physical examination at frequent intervals In reference to number four, our ever improving ability to maintain patients with many chronic disorders in states of relative good health not only introduces the factor of the known degenerative or malignant complications characteristic of these disorders—as is so well exemplified in the instances of diabetes mellitus and pernicious anemia—but also, the masking effect of a second and unrelated disease once the tag' of the initial condition is applied

When confronted with such problem cases, most diagnosticians undoubtedly have various schemes committed either to paper or to memory which they utilize in the expectation that they will at least *think* of the disease It is apparent that both study and experience are prerequisites for the complete disclosure of clinical details, and especially for the employment of this form of analysis, since lacking knowledge of any given disease, one would obviously not know how to seek out its manifestations In an appropriate manner Beecher has commented, "Lacking as we do perfect memories, the fruits of the great sources of knowledge quickly spoil unless they are preserved so in the growth of knowledge, recording (the notebook and pencil) takes rank as a principal aid to the advances of learning Unfortunately, clinical impression represents to the man of short memory the last two or three cases he has seen To the man of longer memory, bias can still distort fact"[1]

To the author's best knowledge, there has not recently appeared a comprehensive and practical paper or treatise on a postgraduate level elaborating this type of an aid to diagnosis. Brief outlines have occasionally been incidentally alluded to, as for example, in recent discussions of amyloidosis[2] and unusual forms of heart disease.[3] I am, therefore, hopeful that this presentation will prove to be both timely and helpful to the interested reader, who is often limited in time, immediate useful references, and methods of approach in dealing with these not too uncommon diagnostic problems. In addition, I feel that a treatise of this order fulfills the long standing need for a convenient "refresher" text in the clinician's own orientation for clinical consultation and for discussion at clinicopathologic conferences. It can also be used to great advantage as a basis for commencing preparation in the examinations on diagnostics given by the various specialty boards.

In this orientation I have found it helpful, when confronted with a given diagnostic problem, to be able to refer to *systematized lists* of those related conditions that are most apt to produce obscure illness. These lists have been carefully considered and molded over the years both from personal experience and from that of my colleagues and divers authors in the management of actual case material. The term "obscure" is broadly interpreted as indicating the presence of one or several pathophysiologic features which have been present for varying periods of time without the clinician being able to pinpoint the cause. Such a nosologic emphasis would therefore obviate a discussion of many acute illnesses. I have departed from this policy in the case of those acute diseases whose atypical features or important complications are infrequently recognized and which require diagnostic differentiation at the earliest moment. For similar reasons, an entire section will be devoted to the problems related to obscure postoperative complications as viewed by the medical consultant—material which is rarely presented in a comprehensive manner with this particular orientation.

This book is not intended to represent an all inclusive treatise on disease. Nevertheless, these listings are designed to be sufficiently panoramic so that those important—albeit uncommon—disease entities which may apply to a given problem patient will be recalled. It is by its very nature in this ever changing age of medical science, practice, and disseminated literature, susceptible to addition or change, particularly as more accurate observations and diagnostic tests evolve. This consideration was ably set forth by Bean in the following remarks: "Since the conserving arts of medicine, though essential, tend to hold back progress if not examined and refreshed by the experiment and experience of practice, and since the essential characteristic of science is that it is provisional, forever being finished but never finished, *change* is the life blood of medicine. But change, unless directed, rarely correlates with progress."[4a]

It is obvious that an author cannot possibly select the material he considers to be essential to a comprehensive presentation which relates to all fields of medical and surgical interest without being influenced by his own personal experience and interests. I have attempted to minimize unnecessary bias and to intersperse as little personal conviction as possible

among the facts and generally accepted observations These efforts are at once defeated, however, by the nature of certain subject material, as in the general discussions relating to iatrogenic illness and the potential scope of the "diseases of maladaptation" Similarly, where my experience has pointed out the need for stressing certain considerations that tend to be overlooked in a number of important clinical disorders (such as "intractable heart failure" and unrecognized pyloroduodenal obstruction), I have done so

In general, only a limited number of pertinent remarks and references relating to the individual diseases appear in each major grouping Since it is assumed that the reader has become sufficiently experienced in the performance of a careful history and physical examination, in the interpretation of the majority of the numerous and diverse laboratory aids which are generally available, and in the appreciation of both the classification and natural course of most diseases, this abbreviated discussion seems justified in keeping with the aims of the book A somewhat greater elaboration will be set forth, however, in the case of those conditions which are infrequently encountered, commonly overlooked, not well comprehended, or insufficiently stressed by most physicians While this book is presented chiefly as an effort along diagnostic lines, significant and related therapeutic observations that merit emphasis are occasionally introduced

I should like to stress that it is *not* the fully developed classic syndromes with which we are necessarily concerned here, but rather their earlier, atypical, or "formes frustes" manifestations This is particularly so in the case of the more common diseases For example every clinician can poignantly recall specific baffling cases of "apathetic" hyperthyroidism, hematogenous tuberculosis, hypernephroma, "preleukemic" leukemia, and myeloma in their presenting symptom complexes—not to mention the "fevers of unknown origin"—in this regard The listings and commentary become less esoteric if these experiences are kept in mind Furthermore the author wishes to emphasize that this volume is *not* intended to serve primarily as a textbook on rare diseases

Inasmuch as there appeared to be no single method for achieving the scope of this treatise, other features have been incorporated and utilized in addition to the listing and discussion of the various disease entities The *differential diagnosis* of several clinical manifestations which frequently are the presenting features of systemic disorders are accordingly included Among these signs and symptoms are hypermetabolism fever cardiomegaly, and polyneuropathy These résumés are utilized primarily as a means of drawing the attention of consulting physicians to certain valuable clinical clues in the analysis of an obscure systemic illness In several instances—most notably pneumonitis, meningitis unexplained heart failure hepatitis, mediastinal tumors, fever associated with a heart murmur, and splenomegaly—a more detailed discussion is included by virtue of the relative importance and frequency of these particular findings

Similarly, when the patient does not exhibit the anticipated response to conventional treatment in several very important disorders, the author has found an *analysis of the possible complications and the therapeutic measures employed* to be a fertile field for discussion Such would apply in par

ticular to congestive heart failure myocardial infarction, and diabetic acidosis—situations wherein the medical consultant is frequently asked to express his opinion concerning the possible deleterious effects of the therapy itself These discussions are further supplemented by the chapter on Iatrogenic Illness (Group XIII)

Another oft neglected technique that is profitably utilized by master diagnosticians is the emphasis upon the *familial predisposition to disease in "asymptomatic" relatives* Since rheumatic fever, thyrotoxicosis, pernicious anemia, the hemolytic anemias, diabetes mellitus, hypercholesterolemia, and certain neurological states have been conclusively shown to exhibit striking genetic linkages—to cite but a few of the more common instances—the astute physician would do well to apply this same approach more frequently It is to this type of observer that we are indebted for further pathogenetic and diagnostic insights into chronic relapsing pancreatitis diabetes insipidus, periodic disease, various disorders of metabolism, and many other entities (including drug reactions) which occasionally turn out to have interesting genetic constellations and familial ramifications The increasing importance to the clinician of epigenetics (i e , the study of how a gene produces its effects in the individual) and the molecular concept of hereditary disease are further discussed under Group XIV

The *cutaneous manifestations of disease* will be stressed, inasmuch as the concept of "dermatopathology as a window to systemic illness" has repeatedly proved itself to be a rewarding one in the hands of alert clinicians My conviction concerning the importance of this particular phase of diagnostics is asserted by the inclusion of Group XVII, entitled "Cutaneous Medicine " Reference to the appropriate illustrations in the Atlas included in this group are incorporated throughout the text

An additional useful approach in the fulfillment of this book s purpose is the *listing, classification and concise analysis of the numerous laboratory and clinical diagnostic procedures* which are available to most clinicians These considerations are set forth in Part II and they will be further discussed in the introductory remarks to that section Reference to the page numbers on which these diagnostic aids are found also appear throughout the text Elaborate charts diagrams x rays electrocardiograms, and other mnemonic aids (all of which can be obtained in the standard textbooks of medicine or differential diagnosis) have been avoided throughout both main sections

I have also purposely omitted the presentation of interesting and instructive case reports as a means of presenting diagnostic approaches to specific problems for two reasons First, the proportions of this volume would increase to the point of interfering with the practitioner's ability to get at the "meat of its content Secondly, the bibliography not only abounds in references to detailed descriptions and analyses of unusually interesting case material but also includes a large number of the Cabot Case Records of the Massachusetts General Hospital that have appeared in the *New England Journal of Medicine* The latter were carefully chosen over a ten year period for their great value in illustrating many of the considerations elaborated upon in the clinical discussions within this text

The *reference bibliographies* of Part I and Part II have been care-

fully screened for content, accuracy, and availability The great majority of the articles cited have appeared in the standard American medical journals within the past ten years The references in this edition are carried through to October, 1957 Lacking the awareness of a better, more recent, or more readily available paper on certain subjects, it was occasionally necessary to include a report which had been published either some time ago, or in a foreign (usually British) or less widely distributed journal

Wherever possible, however, emphasis is placed upon the more recent contributions and critical reviews on a particular subject, rather than again repeating references to original classic treatises which appeared several decades ago The latter can nearly always be found in these review articles and in the standard texts Few books are included as references inasmuch as the information in the current journals is generally either more detailed, more up to date, or more readily available It is hoped that additional or substituted references, both by the reader and by the author in subsequent revisions of this book will compensate for those which will inevitably become antiquated

The many references to papers published in the various journals of radiology serve to point out the great wealth of clinical material that clinicians can derive from this source Similarly, the inclusion of a number of papers dealing with basic biophysiological and clinical research serves to emphasize the keener appreciation which the study of these efforts can contribute to the understanding and "practical" management of diagnostic and therapeutic problems It also emphasizes the folly of attempting to dissect or to separate these disciplines too closely This type of fundamental insight into pathogenetic mechanisms has frequently transformed the clinician's apathy towards a particular disorder into one of sheer excitement, and has afforded these physicians the added mental stimulation and satisfaction in their practice that inevitably accompanies such comprehension and interest

Considerable deliberation was frequently engaged in concerning the great length of the bibliography I finally concluded that it would be detrimental to the value of this type of a panoramic but abbreviated text if the consultant physician or interested reader could not readily find the authoritative source material once his curiosity and intellectual appetite for a particular subject had been whetted by the short-running commentary

I am grateful to many of the authors whose names appear in the two bibliographies for their kindness in sending me reprints of their papers—often at considerable expense and effort My gratitude also extends to the many teachers, colleagues and authors from whose experience I have gleaned many of the diagnostic gems concepts, and axioms that are reproduced in this book without specific reference because of the physical limitations necessarily involved

One of the great advantages and blessings to physicians in the current era is to be found in the readiness and rapidity with which the medical literature and scientific advancements can reach them, wherever they may be Similarly, we should be appreciative of the relative ease with which the members of our profession can attend seminars and conventions in dis

tant cities, opportunities that were afforded to but few busy practitioners only a short time ago I attribute the ability to have assembled this work in a small community, and in the absence of an active affiliation with either a medical school or a teaching hospital at the time, in large measure to these technical advantages of our time

There are several comments in order at this point concerning the location of source material which cannot be readily located or obtained While the periodical literature pertaining to medicine currently approaches 10 000 publications throughout the world, we are fortunate in having a coverage of over 1300 of the key periodicals by the two major medical indexes in the United States These consist of the *Quarterly Cumulative Index Medicus* (*QCIM*) that covers over 800 medical publications (with particular emphasis on the Latin American journals), and the *Current List of Medical Literature* (*CLML*) which encompasses more than 1000 medical periodicals The QCIM appears about two years after the publication of the original articles, whereas the indexing in the CLML is on a monthly basis with a cumulative index appearing semiannually

Two other fine ources for borrowing original domestic and foreign periodicals or books are the National Library of Medicine in Washington, D C —which constitutes the largest medical library in the Western Hemisphere—and the Library of the American Medical Association (535 North Dearborn Street Chicago 10, Illinois) Loans from the former can be made only on an interlibrary loan basis, whereas members of the American Medical Association can borrow periodicals directly from the latter for five days free of charge (There is a fifteen cent charge in stamps for each item borrowed by nonmembers) Photoduplications services are available from the National Library of Medicine

Attention is directed to the *special index of the signs, symptoms important laboratory manifestations, and significant associations of certain disease entities* that pertain to those puzzling diseases discussed in the text While this index is not intended to serve as an exhaustive outline of both physical diagnosis and differential diagnosis, it can be of considerable value to the clinician who is confronted with such problems, both as a guide in itself and as yet another key to using the book

One must naturally be aware of the following *shortcomings* in the approach to diagnostics used here The wizened and humble diagnostician appreciates more than do most others Oscar Wilde s quip to the effect that ' experience is the name everyone gives to his mistakes

First, as a result of his reading and training particularly at clinicopathologic conferences the physician tends to attribute all the patient's symptoms to one disease entity By following this pedagogic rule too closely in practice he may readily overlook other concomitant and treatable organic or emotional afflictions

Secondly the temptation might occur to "fit the patient to the disease This is an unfortunate situation if in either the "riding of a hobby ' or the grasping at straws," one overlooks the more common and probable conditions, and subjects his patients to undue expense, anxiety and potential physical danger (as with excessive diagnostic radiation or from anaphylactoid reactions to test substances) We are all

aware of certain patients with the hyperventilation syndrome, minor electrocardiographic abnormalities, and nonarticular rheumatism, for example, who travel from one diagnostic clinic to another as a result of having originally been given an erroneous organic diagnosis

Thirdly, there can be no short cuts to accurate diagnosis without the collection and careful, systematic and logical analysis of as many facts as can be obtained concerning a given case, depending on both circumstances and the urgency of the problem It is apparent that those clinicians who enjoy the respect of their colleagues as astute diagnosticians usually achieve this status primarily as a result of the time and interest they give their patients This does not doubt the propriety for the clinician of experience to occasionally trust and respect his intuitive "hunch" about the nature and management of an obscure illness In fact such perception is often necessary, so that a seriously ill patient will not suffer further from over rationalized diagnosis or treatment (This is well exemplified by the prolonged withholding of antibiotics or by the undue delay in performing a laparotomy for persistent abdominal pain that is occasionally encountered in patients with either diabetes mellitus or the sickle cell trait)

Bearing all these considerations in mind, one stands to gain much from this type of orientation and aid in diagnostics Most significant of all is the possible opportunity afforded of being able to offer the patient with an obscure symptom complex a specific therapy—if not a cure—when others have not been able to do so because of an incorrect diagnosis The continual improvement of one's diagnostic skills derived from "pearls" relating to history taking and physical diagnosis, along with the capacity of being able to extract the greatest help from the least amount of laboratory work, is inherent in this attitude Finally, as he reads the literature with greater interest and keenness in an active attempt to add constantly to this foundation one succeeds in evolving a truly personal and integrated approach to the diagnostics of medicine

The basic philosophy of the approach set forth in this treatise can be summarized in the following words of Burchell

> I am in general accord with Hutchison's Don'ts for Diagnosticians the first two of which read Don't be too clever and Don't diagnose rarities Hutchison himself quoted Samuel Gee who said Common things most commonly occur and it may be emphasized that many rare conditions perhaps could be all but forgotten without loss in day to-day practice Unusual manifestations of common diseases probably mislead the physician more often than do unusual diseases Rare conditions tend to be the spice of practice however and constitute the substratum whereon one's probing wits are tested To a certain extent also missing the diagnosis of a rarity is the *bête noir* of the specialist Moreover in this era of rapid transportation the patient who has sought diagnosis without success often travels far looking for special help [*]

PART ONE

Groupings of Related Diseases Frequently Producing Puzzling Illness

GROUP I

Endocrinopathies

GENERAL CONSIDERATIONS

ADRENOCORTICAL INSUFFICIENCY

Primary Symptomatic Therapeutic iatrogenic Hypoaldosteronism

HYPOTHYROIDISM

Primary Symptomatic Therapeutic iatrogenic

HYPERTHYROIDISM

Primary Adenomatous Factitious

Hypermetabolism

HYPERINSULINISM

Single or multiple adenomata Factitious The Zollinger Ellison syndrome

Hypoglycemia

The Houssay phenomenon in man Diabetes mellitus Non pancreatic neoplasms Hepatic hypoglycemia

PHEOCHROMOCYTOMA

HYPERPARATHYROIDISM

Primary Secondary Multiple endocrine adenomata

Osteoporosis

Osteomalacia

Hypophosphatasia

HYPOPARATHYROIDISM

Primary Post-thyroidectomy

Pseudohypoparathyroidism

Unexplained tetany

THE ADRENOCORTICAL HYPERFUNCTION SYNDROMES

The Cushing syndrome Primary aldosteronism

THE ANTERIOR PITUITARY HYPERFUNCTION SYNDROMES

"Fugitive acromegaly"

THE PITUITARY HYPOFUNCTION SYNDROMES

Sheehan s syndrome Symptomatic thyroid and adrenal insufficiency Multiple glandular sclerosis Diabetes insipidus

THE MENOPAUSAL SYNDROMES

Premature menopause Nonendocrinologic systemic causes of excessive uterine bleeding Muscular dystrophy Severe infectious hepatitis Keratoderma climactericum Osteoporosis

OTHER OVARIAN SYNDROMES

The Meigs Cass syndrome Krukenberg tumors Functioning tumors The Stein Leventhal syndrome Ovarian hyperthecosis Primary ovarian agenesis or arrest

ONE NEEDS only to consider the very nature of the blood borne hormones to appreciate the profound constitutional changes that their absence or overproduction can evoke physiologically and biochemically The loss of the normal degree of homeostatic checks and balances along with the presence of pluriglandular disturbances compounds this problem for the body Although the classic manifestations of the majority of the diseases to be discussed can be accurately cited by most physicians, it is remarkable how long a patient with fairly typical myxedema or the Cushing syndrome can be seen, for example before the diagnosis "rings a bell" In this group of disorders, the importance of a clear comprehension of the clinical and biochemical variants has been particularly emphasized by the continuing increase in the number of potent therapeutic hormones antimetabolites and antienzymatic agents the intelligent administration of which is mandatory

The endocrinopathies have also been presented first because both specific diagnostic tests and treatments are now available for practically every condition described A listing and analysis of the more valuable procedures that are usually available in the evaluation of suspected endocrinopathies is presented in Section V of Part II (Studies of Endocrine Function) In addition to the accurate performance of these divers tests the importance of the correct collection and transportation of the specimens cannot be overemphasized especially when dealing with gonadotropin assays

While such manifestations as hypermetabolism, hypoglycemia, osteoporosis, osteomalacia, and unexplained tetany are not necessarily associated with true endocrinopathies the frequency with which this relationship does exist warrants their inclusion in this chapter

ADRENOCORTICAL INSUFFICIENCY

Adrenocortical insufficiency has assumed a wide range of interest in recent years notwithstanding the concurrent decline in the incidence of tuberculosis Metastatic carcinoma selective cortical necrosis and atrophy histoplasmosis and amyloidosis of both the primary and secondary types have received increasing attention for their roles in producing Addison s disease [5] Although metastatic carcinoma in the adrenal glands is commonly encountered by the pathologist, it is infrequently diagnosed clinically because patients usually succumb from other causes before the characteristic

features of adrenal insufficiency appear, and because the cancerous cachexia can mask addisonian manifestations Unilateral or bilateral adrenal metastases were noted in 32 9 per cent of autopsies in patients dying from carcinoma at one institution over a five year period, with the primary sites being equally distributed among the lung the large bowel, and the stomach [5b]

In the presence of unexplained weakness, fatigability, loss of weight, hypotension, and anemia, *the diagnosis of Addison's disease must always be considered* The mental changes of restlessness, apprehension, and increasing irritability are at times quite striking There may be a marked sensitivity to the opium alkaloids Salt craving and an unusual intolerance for fasting even over brief periods are suspicious addisonian clues If the history of a previous hypertension is not obtained, the presence of normotension rather than hypotension might prove misleading Every experienced surgeon and gastroenterologist can recall instances of the patient with nausea, vomiting abdominal pain or costovertebral angle tenderness who turned out to have Addison's disease rather than an acute condition in the abdomen or the irritable bowel syndrome

In considering *symptomatic adrenal insufficiency* its relationship to both the anterior pituitary and thyroid may present itself as a component of the following three complexes (1) primary pituitary failure,[98] (2) *independent primary hypofunction of both the adrenal and thyroid glands* (the Schmidt syndrome) [7] and (3) primary thyroid hypofunction with secondary adrenal insufficiency [6, 8] Furthermore, well documented concomitant but etiologically independent diabetes mellitus and Addison's disease have been observed in the absence of pituitary disease and hemochromatosis [9, 10] In one report of six cases in which the diabetes antedated the adrenal insufficiency, the required dose of insulin was reduced in four instances and increased in two [11] On rare occasions Addison's disease has also independently complicated idiopathic hypoparathyroidism [12] It is of interest that the latter state is not necessarily ameliorated by the administration of cortisone It has also been suggested that the triad of familial juvenile hypoadrenocorticism hypoparathyroidism and superficial moniliasis constitutes a specific syndrome [1c]

In the patient with known Addison's disease the appearance of unexplained symptoms, increased hormonal requirements, fever, tachycardia, leukocytosis with a relative lymphopenia and an elevated sedimentation rate suggests the presence of either active tuberculosis or another type of infection [14] While there may be considerable cellular infiltration of the adrenals associated with extramedullary hematopoiesis in myeloid metaplasia (myeloproliferative disease), an ensuing adrenal insufficiency is usually due either to hemorrhage within the gland or to thrombosis of the adrenal veins with infarction of the gland [739]

The skin in Addison's disease has a soft texture and may or may not show the pigmentation of the nipples, scars, knuckles creases, exposed parts and mucous membranes The actual color can vary from bronze to dark or mulatto-like it is due to the presence of both melanin and melanoid in excessive amounts One should not overlook the vitiligo or the large black nevi ("ink spots") that occasionally rapidly develop and

precede the generalized pigmentation It is emphasized that the pigment is not histologically specific and that characteristic addisonian pigmentation may normally be present in Negroes[15]

The manifestations of Addison s disease in the skin and mucous membranes are depicted in Figures 55 and 56 (Atlas pages 35 and 36)

The *long range effects of cortisone and corticotropin therapy* are currently of paramount importance The withdrawal of these agents in patients who have been kept in a state of chronic hypercortisonism might result either in an adrenal crisis[16] or in a severe panangiitic reaction that carries all the risks of systemic lupus erythematosus or polyarteritis if the corticoids are not readministered[17] Unlike the flare-up of rheumatoid arthritis (which primarily affects the joints and fibrous tissues), the musculoskeletal manifestations of chronic hypercortisonism are more diffuse and generalized, and are usually associated with cutaneous and subcutaneous hypersensitivity

Furthermore, it has been shown that in certain susceptible patients with rheumatoid arthritis (and possibly disseminated lupus erythematosus), the administration of cortisone might precipitate the development of a diffuse necrotizing arteritis closely resembling classic polyarteritis nodosa, especially when signs of chronic hypercortisonism were also induced[18] Such widespread vascular lesions—which are rarely encountered in patients with rheumatoid arthritis in the absence of steroid therapy—took place even though there was no reduction in the dosage The high incidence of peripheral neuritis as a clinical manifestation of this 'panmesenchymal reaction' is noteworthy

Another interesting complication is encountered in children with acute rheumatic fever receiving excessively large doses of prednisone The cessation of this therapy has resulted in a syndrome characterized by intense pruritus painful erythema nodosum like lesions of the skin, and an extensive panniculitis[18a] In children being treated with cortisone, especially under the age of eight years, hepatomegaly due to fatty infiltration commonly occurs This might pose an important consideration, inasmuch as the large liver could be misinterpreted as evidence of congestive heart failure in the patient being treated for acute rheumatic fever[18b]

More significant, however, is the very disturbing fact that at present it is impossible to predict either which patients are liable to postoperative adrenocortical insufficiency as a result of preoperative hormonal treatment, or the minimal and maximal periods of the ensuing suppressive effect on adrenal function by therapeutic hypercortisonism[20] It should be borne in mind that therapeutic hypercortisonism resulting from the use of cortisone or its analogs represents the composite of exogenous hypercortisonism and endogenous hypocortisonism in contrast to corticotropin induced hypercortisonism which consists of endogenous hypercorticalism and endogenous anterior hypopituitarism[17b] Cortisone, its analogs, and ACTH are all known to be capable also of suppressing the function of the thyroid gland[19]

The profound and prolonged nature of the "compensatory" adrenal atrophy that can occur either as a result of long standing steroid therapy, or in the contralateral adrenal in the patient with an adrenal tumor which

is secreting excessive corticoids, requires active consideration in the management of these patients The reversal of the corticogenic adrenal atrophy by the administration of exogenous ACTH can be effectively achieved only by the very gradual reduction in the dose of the adrenal steroid being employed, along with repeated intermittent courses of ACTH in high dosages [15b] Fortunately, there have been no well authenticated instances of acute adrenocortical failure following the abrupt withdrawal of ACTH or during periods of stress in a corticotropin treated patient [15b]

Fatal unrecognized disseminated sepsis by the tubercle bacillus, other bacteria, viruses (especially herpes zoster), and the various "opportunistic" fungi has developed during treatment with cortisone [508, 513] The glomerular thrombosis and tubular necrosis found at autopsy in many of these cases are similar to the lesions encountered in the kidneys of cortisone-treated rabbits following endotoxin administration [21] It is highly important to distinguish the septic arthritis that can complicate steroid therapy from a *pre-existing lupus erythematosus or other arthritic process for which the* patient is receiving such hormonal therapy The remarkable absence of fever and local pain in the former instance can lead to extensive damage, which might be obviated by an early diagnostic aspiration of the joint in question [21d]

While there are a number of reported instances in which ACTH or the adrenocortical steroids were of apparent great value in the clinical management of patients with massive necrosis of the pancreas, one should also consider that these agents may produce damage to the pancreas *per se* Carowe and Liebow were impressed with the lesions found in this gland both in animals and in 51 postmortem examinations where such therapy had been used These consisted chiefly of ectasia of the pancreatic acini acute pancreatitis, or peripancreatic fat necrosis [115c] The investigators postulated that the adrenal steroids may alter the pancreatic secretion and effect obstructive acinar changes along with a release of pancreatic enzymes It is a subject for conjecture at present as to how many individuals who *experience abdominal pain vomiting, and fever while on* steroid therapy may actually be having mild bouts of pancreatitis

One of the drawbacks to the use of fluorohydrocortisone and other corticoid derivatives whose sodium retaining activity may exceed that of cortisone acetate by over one hundred times is the readiness with which overdosage resulting in hypertension, edema, or angina can be produced The increasing problem of "steroid ulcers" is discussed under Group XVII (p 499)

Several unusual disorders actually resulting in *chronic sodium depletion* may simulate adrenal insufficiency These include the so-called salt losing nephritis [22, 23] small congenital medullary cysts in the kidney,[24] and the hyponatremia associated with pulmonary or central nervous system tumors in the presence of normal appearing kidneys and adrenals Further comment is directed to these disorders in the ensuing text (pp 52 and 81)

Not only will the subject of excessive aldosterone production be intensively explored in the near future but also that of clinical *hypoaldosteronism* One instance has already been reported in which "pure hypoaldo-

steronism was implicated in the presence of normal production of the other adrenal steroids This individual experienced repeated bouts of cardiac standstill that were attributed to the effects of spontaneous hyperkalemia on a pre existing complete atrioventricular heart block [82] The associated defect in potassium excretion became most evident on a low sodium diet The diagnosis appeared to be quite feasible when very low levels of urinary aldosterone were found both before and after sodium restriction

HYPOTHYROIDISM

Concerning "subclinical hypothyroidism, it should be emphasized that this state is *not* synonymous with hypometabolism [27a] If one treats the latter with thyroid hormone, the patient is trapped in the vicious cycle of involutional atrophy and iatrogenic disease The usual parameters of thyroid function (i e , the protein bound iodine, cholesterol, and 24 hour thyroidal uptake of I^{131}) have generally been within normal limits in individuals with "euthyroid hypometabolism' (patients with basal metabolic rates below −20 per cent) Nevertheless there may possibly be an abnormality in the thyroxine metabolism of these individuals as indicated by infusion studies with I^{131} labeled l thyroxine [b]

One must be aware that myxedema often first presents itself in as many unusual ways as does adrenal insufficiency Gastrointestinal complaints, [8] tinnitus or deafness, effusions into the pericardial pleural and peritoneal cavities [28] a true delirium [30] coma, severe headaches anemia, angina pectoris hirsutism in children [31] atypical facial neuralgia,[32] and an exaggerated response to many drugs (particularly the opiates) are but a few that come to the experienced clinician s recall The gastrointestinal manifestations of myxedema include not only constipation, flatulence and ileus but even a megacolon-like syndrome [28] There may be extensive cutaneous dermadromes including isinglass-like pretibial scaling xanthomatous lesions, sparse brittle hair and dystrophy of the nails

The interesting pseudomyotonia of myxedema is readily detected by the delay in relaxation of the tendon jerks [29] This sign is regarded as diagnostic of this condition by some observers It differs clinically from true myotonia in that it is not associated with the actual symptom of difficulty in relaxing contracted muscles that is so characteristic of the latter disorder The association of myasthenia gravis with either spontaneous or surgically induced myxedema is even rarer than the association of this specific myopathy with thyrotoxicosis Three instances of this phenomenon have been reported from the Mayo Clinic but are regarded as being probably a coincidental occurrence [29b] The demonstration of the aforementioned characteristic slow relaxation of the muscle stretch reflexes associated with hypothyroidism may be used to differentiate these two processes (the reflexes being normal in myasthenia gravis)

It is not generally appreciated that hypertension can coexist with myxedema, although there is usually a narrow pulse pressure Profound myxedema can occur in the presence of relatively normal plasma cholesterol levels due to the wide normal range of this blood constituent (a determination subject to much technical error) Even under these circumstances,

however, the level often still drops by as much as 45 per cent with treatment[33]

Further studies in recent years have made it increasingly apparent that struma lymphomatosa (Hashimoto's disease) is not a true thyroiditis, but a pituitary TSH mediated compensatory reaction to the absence of thyroid hormone production[34] Accordingly the indicated therapy is desiccated thyroid and not surgery or irradiation

It may be difficult initially to distinguish the patient's physical appearance (particularly the yellowish hue to the skin) and the associated anemia in this disorder from that of both uremia and pernicious anemia until other studies are carried out Hypothyroidism and renal disease have several clinical features in common including periorbital edema, lassitude, weakness, and anemia In view of this overlapping it is helpful to bear in mind that albuminuria usually does not occur in uncomplicated hypothyroidism, nor is there unequivocal clearing of the albuminuria on thyroid therapy if the disorder is due to complicating renal vascular disease[35]

Just as in the case of cretinism prompt recognition of juvenile myxedema is imperative if serious growth and mental retardation are to be prevented There is ample clinical and genetic support for the concept of hereditary transmission of sporadic (nonendemic) cretinism with goiter based on the high familial incidence the frequently encountered consanguineous background and the specific arrest of thyroid hormone synthesis that is demonstrable at one of several stages[3]

One must also give much thought to the possibility of *symptomatic hypothyroidism* in order to anticipate and prevent the precipitation of such a patient into an acute adrenal crisis by the sole administration of thyroid hormone, even when given in small amounts The very characteristic (but transient) severe reaction to thyroid hormone which precedes the clinical improvement on this medication in patients with primary myxedema should not be misconstrued as an adrenal crisis In fact, this response tends to confirm the diagnosis of hypothyroidism clinically Very low TSH values have been encountered in primary myxedema when severe liver disease was also present This observation stems from the inability of the diseased hepatic parenchyma to inactivate estrogen, allowing it to accumulate in the circulation and to depress the production of TSH[37]

Another commonly unrecognized cause of *inhibition of thyroid gland function* is the prolonged administration of thyroid substance (the Farquharson phenomenon)[36] The goitrogenic effect of therapy with cobalt, phenylbutazone PAS and thiocyanate preparations are discussed in a later chapter (p 394) Myxedema or goiter or both have been observed to follow the prolonged use of various iodide preparations (potassium iodide, syrup of hydriotic acid Lugol's solution) particularly in the treatment of chronic bronchial asthma[38] It is felt that the iodide exerts this effect in several ways (i e, slowing the rate of release of formed thyroid hormone, and blocking the organic binding of elemental iodine and of thyroid hormone synthesis due to the persistent elevation of the serum iodide level)[39] This role of the iodides is undoubtedly overlooked in some patients who are misdiagnosed as having thyroiditis or spontaneous myx-

edema In most instances, reversion to a euthyroid state will ensue after cessation of the aforementioned therapy

HYPERTHYROIDISM AND HYPERMETABOLISM

If only by virtue of its frequency and curability, *hyperthyroidism should be actively suspected in every case of undiagnosed or unresponsive* heart failure, rapid heart action, auricular fibrillation, myopathy, and recent unexplained mental aberrations (particularly overactivity, phobias, and apprehension) It is characteristic in the early phases of this illness for the patient himself to deny feeling ill or to have but few complaints, but unlike the neurotic, he is often prompted to seek medical aid by others The existence of heat intolerance may be very subtle, especially in the cooler climes, but can usually be elicited by the alert diagnostician The following atypical features often tend to obscure the diagnosis of hyper thyroidism a normal or slow pulse rate progressively increasing weight or even obesity, the absence of a palpable thyroid gland, an apathetic demeanor of the patient and a normal metabolic rate[40] It has been the author s experience that in the "borderline" cases of hyperthyroidism where the help from the laboratory is most needed, the results forthcoming are most apt to be equivocal, even when refined chemical and radioiodine studies are utilized

On occasion hyperthyroid patients have also presented themselves with a resistant type of periarthritis of the shoulder, uncontrolled diarrhea, osteoporosis and fractures due to the excessive loss of calcium and phosphorus other rheumatic states albuminuria, bulbar paralysis convulsive seizures, and abdominal pain simulating gallbladder disease, peptic ulcer or pancreatitis[40] Both nondiabetic glucosuria and the precipitation of true clinical diabetes mellitus may be produced by hyperthyroidism

A number of these patients have been described with either a periodic muscular paralysis or a chronic myopathy associated with weakness and wasting of the proximal muscles of the pectoral and pelvic girdles which disappeared following thyroidectomy[40b, 41] While myasthenia gravis differs from the thyrotoxic myopathy in a number of respects, particularly the predominant involvement of the bulbar and ocular muscles and the absence of obvious atrophy the two disorders may be observed in the same patient In such instances, treatment directed to the thyrotoxicosis will usually ameliorate the myasthenia and improve the patient's response to prostigmine[40b] However a "seesaw" relationship between the thyrotoxicosis and myasthenia gravis has been encountered (i e the myasthenia becoming aggravated as the thyropathy is controlled)[29b]

The nosologically misleading entity of "pretibial myxedema" will not be diagnosed in the absence of exophthalmos if hyperthyroidism *is not* considered This dermatosis consists of circumscribed, elevated, nonpitting, yellowish to reddish brown plaques over the anterior tibiae that may be tuberous or resemble pigskin Melanin hyperpigmentation (occasionally very marked on the eyelids), a persistent red dermatographia of the skin over the thyroid, alopecia areata and vitiligo are also observed in hyper thyroidism

The nail changes in hyperthyroidism and circumscribed pretibial myxedema are depicted in Figures 31 and 53 (Atlas pages 20 and 33)

The most interesting observations of five cases of hyperthyroidism following bilateral parotitis and other forms of salivary glandular disease at one clinic, and radiation parotitis from I^{131} therapy at another, may be more than coincidental [42] It is well known that iodides are concentrated by the salivary glands and are found in the saliva Moreover, it has been suggested that the salivary glands are actually "reverse thyroid glands" (i e, active in breaking down the thyroid hormone) [43a] In one study, however, there was no evidence that the salivary glands deiodinated thyroxine even though the salivary I^{131} bore a nearly constant relationship to plasma inorganic I^{131} [43b]

Reserpine can exert a profound ameliorating effect upon the clinical course of the patient with thyrotoxicosis but does not influence the size of the thyroid gland, the 24-hour uptake of radioactive iodine, or the levels of the protein-bound iodine [44] In view of both the close resemblance of this disorder to anxiety states and the widespread use of this tranquilizing agent in the treatment of nervous individuals, one readily appreciates the potential diagnostic difficulties that clinicians are apt to encounter when the hyperthyroidism is so masked

Factitious hyperthyroidism is by no means a rarity It should be sought out in those cases where symptoms persist after what should have been adequate surgery or radioiodine treatment, or where a very high total urine iodine level is found in the presence of a markedly decreased uptake of radioactive iodine [45]

The numerous extrathyroidal causes of *hypermetabolism* have been adequately classified and discussed by Bruger and Hollander [46] Acromegaly, pheochromocytoma, anemia polycythemia, leukemia the lymphomas congestive heart failure aortic stenosis, arteriovenous aneurysm myeloma, Paget s disease of bone, hemochromatosis, drugs diffuse erythrodermas, and fever are among the commoner conditions that have at times been mistaken for thyrotoxicosis Paradoxically, hyperthyroidism can definitely be present without apparent hypermetabolism [47]

HYPERINSULINISM AND HYPOGLYCEMIA

Whipple's criteria for the diagnosis of *hyperinsulinism* would seem to be fairly clear cut in appraising the patient who is experiencing recurrent hypoglycemic symptoms (i e, attacks occurring with the patient fasting, repeated blood sugar levels below 50 mg per 100 ml, and a prompt response to the administration of glucose) [48] This entity is nevertheless still infrequently considered in the differential diagnosis of recurrent seizures and coma mental aberrations, and visual disturbances such as diplopia, until either marked obesity or profound brain damage has already occurred [49, 50] The absence of symptoms before breakfast and the reproduction of symptoms by hyperventilation are helpful clues in clinically separating this entity from functional hyperinsulinism [51] The combination of fasting and muscular work may reinforce their effects and bring out a latent case of hyperinsulinism [56]

Contrary to a widespread belief, it should be noted that there is no characteristic glucose tolerance test in this disorder If a concomitant hypercalcemia is found, multiple adenomas of the parathyroid and pituitary glands coexisting with adenomas of the islets are to be considered [52] Mulder and his colleagues have reviewed a series of 20 patients with the syndrome of *distal muscular atrophy and paresthesias secondary to hyperinsulinism* ("hyperinsulin neuronopathy") [55]

If no pancreatic tumor is found at operation in the presence of typical hyperinsulinism a thorough search for islet cell neoplasms in heterotopic pancreatic tissue should be made [54, 56] Attention is directed under Group XV to the several important considerations with which surgeons must cope during a fruitless search at laparotomy for a pancreatic adenoma (p 472) The possibility of a *factitious hyperinsulinism* must be considered and pursued in *every* nurse or relative of a diabetic who exhibits recurrent hypoglycemia, no matter how vigorously the self administration of insulin is denied

Increasing interest has been focused more recently on other functioning pancreatic tumors, resulting in the *Zollinger Ellison syndrome* [53] This is characterized by the triad of a pancreatic adenoma (possibly composed of alpha gamma, or delta cells) an intense ulcer diathesis, and gastric hypersecretion The degree of gastric hypersecretion that can be produced by these pancreatic tumors is exemplified by the report of as much as 9 liters of highly acid gastric aspirate in one such patient whose attacks of diarrhea required constant gastric suction for control [53d]

While it is well known that significant hypoglycemia from any cause has a deleterious effect upon individuals with an ulcer diathesis because of the ensuing hyperacidity hypertonicity and hyperperistalsis, only 3 of the 24 cases of the Zollinger Ellison syndrome reported to date have exhibited hypoglycemia [53c] A large number of these adenomas have proved to be malignant The surgeon who is confronted with multiple ulcerations in the stomach, duodenum, and jejunum should be very suspicious of an underlying pancreatic tumor, particularly when stomal ulcers develop in spite of extensive ulcer surgery and intensive postoperative medical treatment Even if no tumor can be found, Zollinger recommends a radical resection of the body and tail of the pancreas under these circumstances

A brief discussion of several other causes of *hypoglycemia* is in order When a diabetic becomes very sensitive to insulin and responds poorly to intravenous glucose, a complicating *panhypopituitarism or adrenocortical insufficiency* may be present [58] I recently observed such a patient with widespread carcinomatosis originating from the urinary bladder The importance of this *"Houssay phenomenon in man"* is stressed again under the anterior pituitary hypofunction syndromes The clinician should always bear in mind the seemingly paradoxical background of early clinical *diabetes mellitus* in patients experiencing hypoglycemic episodes [59] During the course of an oral glucose tolerance test, mild diabetes with a secondary *symptomatic hypoglycemia is found to differ from* functional hyperinsulinism in the following respects the peak venous blood sugar concentration exceeds 160 mg per 100 ml, there is a plateau type curve with persistence of the hyperglycemia beyond the second hour and the fall to hypoglycemic

levels occurs between the third and fifth hours (a finding that is usually noted between the second and fourth hours in functional hyperinsulinism)[55]

It is not generally appreciated that severe hypoglycemia may occur in the presence of various nonpancreatic *neoplasms*, histologically either benign or malignant, and which are not associated with hepatic failure All these reported tumors have been large masses, displacing viscera, and exerting pressure on the posterior abdomen or thorax[56, 60] Persistent hypoglycemia can also be a striking feature in primary carcinoma of the liver, particularly hepatoma, however, the oral and intravenous glucose tolerance studies in these patients are often not unusual[57]

Diffuse hepatocellular damage, hypothyroidism, hypothalamic invasion or destruction Addison's disease, and sprue infrequently produce symptomatic hypoglycemia Nevertheless it is still very important to bear *hepatic hypoglycemia* in mind when confronted with severe nervousness, bizarre neurologic manifestations, peripheral vascular collapse, and coma in patients with liver disease or congestive heart failure All too often, the occurrence of palpitations, sweating, mental clouding, or convulsions in the latter state are attributed to cerebral anoxemia or the underlying cardiac condition while the possibility of hypoglycemia is not even considered Clinicians have long been aware of the fact that there is no constant relationship between the extent of depression of the blood sugar and either the severity of the liver impairment or the hypoglycemic manifestations A therapeutic test with small volumes of concentrated glucose is always indicated when this consideration arises (p 817)[61]

Conn and Seltzer[55] have classified spontaneous hypoglycemia in the following helpful manner

1 *Fasting hypoglycemia* (lowest blood sugar level in proportion to the duration of fasting)

Hepatogenic hypoglycemia
Anterior pituitary insufficiency
Adrenal cortical insufficiency
Central nervous system lesions
Fibromas and sarcomas
Severe renal glucosuria

2 *Stimulative hypoglycemia* (normal levels of the fasting blood sugar, but hypoglycemia occurring two to four hours after the absorption of carbohydrate)

Functional hyperinsulinism
Alimentary functional hyperinsulinism
Hyperinsulinism of infancy

3 *Combined fasting and stimulative hypoglycemia*

Organic hyperinsulinism
Idiopathic spontaneous hypoglycemia of infancy'
Factitious (exogenous hyperinsulinism)

PHEOCHROMOCYTOMA

In a clinical and pharmacologic review of the experience at the Lahey Clinic with the pheochromocytoma problem, there emerged several impressive facts[6] First, all the patients so diagnosed had been initially con-

sidered as probable cases of hyperthyroidism It was only the absence of a significant response to massive antithyroid medication that directed attention away from this diagnosis Secondly, the large number of patients with anxiety states and labile hypertension whose history so closely mimicked that of pheochromocytoma that exploratory operations were required—particularly in the presence of false positive histamine tests—presented an equally sobering clinical dilemma Thirdly, the reliability of the Regitine test becomes considerably impaired when the patient has received either phenobarbital or a rauwolfia preparation, even as long as four weeks previously in the case of the latter drug Unnecessary pneumograms and explorations were performed as a result of obtaining a false-positive test under these circumstances

Fourthly, a number of potential sources for error in the interpretation of retroperitoneal pneumographic studies exist These include the visualization of the fundus of the stomach "on end," an enlarged spleen, the duodenal shadow, and the presence of an enlarged adrenal gland which ultimately proves to be a benign nonfunctioning adrenocortical tumor Fifthly, elevated levels of epinephrine and norepinephrine may not be manifest in the urine When blood assays of these substances are available, it is recommended that they be followed every two minutes after either the onset of the clinical attack or following the intravenous injection of histamine if the other screening studies are inconclusive[62d] The detection of rapid changes in the blood catechol amine levels in this manner will be of particular value in cases of pheochromocytoma of the paroxysmal type Finally, even the urinary catechols have been elevated in some patients solely as a result of anxiety

A number of authors have elaborated upon the differential diagnosis of pheochromocytoma which they have labeled as another "great mimic"[63, 64] The combined renal and hypertensive picture in pheochromocytoma has simulated acute glomerulonephritis[65] Perhaps the predominant release of either epinephrine or norepinephrine might account for the variation and dominance of certain metabolic, hypertensive, and vasomotor features in individual patients Several reports have indicated not only the occasional familial incidence of pheochromocytoma, but also its frequent association with neurofibromatosis and the other neurocutaneous syndromes[66] Since a mild Cushing s syndrome due to adrenocortical hyperplasia has been noted to coexist with a pheochromocytoma, this combination could result in considerable diagnostic confusion[67]

Age does not mitigate against the diagnosis of pheochromocytoma There are 33 cases on record of this tumor in children who were less than fourteen years of age[62e] It is of further interest that multiple neoplasms are encountered in one half of these children

Although the specific pharmacologic diagnosis has been greatly enhanced by experience with both the provocative and phentolamine (Regitine) tests, many patients still die from pheochromocytoma postoperatively or from its cardiovascular complications without the condition having even been considered[68] The Mayo Clinic has recently reported on 15 such autopsied cases, this tumor was listed among the possible diagnoses ante mortem only three times In five instances, death resulted from shock dur

ing incidental operations.[65a] Tomograms taken concomitantly with an intravenous pyelogram might pick up a perirenal tumor more safely than presacral air studies.

It is pointed out that the pathologist may be unable to make an accurate histologic diagnosis of a benign or malignant pheochromocytoma, the latter occurring in approximately 10 per cent of all the cases reported. Eight of 50 patients with pheochromocytoma observed at the Mayo Clinic proved to have malignant tumors, in seven of whom persistent hypertension was encountered.[65c]

In summary, the various tests for pheochromocytoma (see Sections XIV and XVI of Part II) are most profitably carried out in patients who present with the following: spells of severe headache accompanied by profuse perspiration or other vasomotor phenomena, recurrent thoracic and abdominal pain, particularly in the face of hypertension, unexplained nervousness or hypertension in any young and thin hypertensive, no matter how recent, hypermetabolism in the absence of hyperthyroidism, the occurrence of a paradoxical reaction to the ganglion blocking agents, and a rise in blood pressure in response to an anesthetic agent.[65e]

HYPERPARATHYROIDISM, OSTEOPOROSIS, AND OSTEOMALACIA

The importance of parathyroid disease needs no elaboration to those interested in bone disease and renal lithiasis. *Hyperparathyroidism* should be kept in mind in patients with unexplained and pronounced muscular atony, fatigue and loss of weight.[69, 70] A variety of gastrointestinal symptoms has been encountered in patients with this disease (due in large measure to the hypercalcemia); these include unexplained episodes of nausea and vomiting, anorexia, refractory peptic ulcers (*vide infra*), marked constipation, and obscure abdominal pains.[71] While the clinical appearance of acute parathyrotoxicosis may be most dramatic, particularly as evidenced by the disturbed mental function, hyperparathyroidism is essentially a chronic illness.[69, 72]

In addition to the blood calcium and phosphorus determinations, studies of the dental lamina dura and of the urine (if not too dilute) with the Sulkowitch test are available to most physicians. A depressed serum phosphorus level (less than 3.0 mg. per cent) has been found to be a more frequent and reliable clue to the presence of a functioning parathyroid adenoma than hypercalcemia.[69a] Furthermore, the clinician should be cognizant of the potential unreliability of one or two serum calcium and phosphorus levels in the diagnosis of hyperparathyroidism due to the variable individual chemical responses. For example, it is known that not only may a persistently low serum phosphate level occur in the complete absence of a hypercalcemia, but that the serum calcium can exhibit marked variations between normal and high levels within a short space of time, suggesting an intermittent parathyroid hormone hypersecretion.[69b]

While the results of the calcium infusion test are apt to be misleading, the determination of the renal phosphate reabsorption—particularly when studied during a phosphorus deprivation test—can usually establish this diagnosis where doubt exists (p. 726). The phosphorus deprivation test with

its derived phosphorus reabsorption index (P R I) (p 819) may ultimately prove to be of great aid in screening patients with suspected hyperparathyroidism among those presenting with urolithiasis (even when normocalcemia and a normal 24 hour excretion of calcium are present), unexplained bone disease, hypercalcemia, intractable peptic ulcer, and among the relatives of patients with parathyroid adenomas In contrast to the possible lowering of the hypercalcemia associated with sarcoidosis and other causes by the administration of cortisone, no such response in the serum calcium is forthcoming in patients with hyperparathyroidism

In the presence of hypoglycemia and hyperparathyroidism, familial multiple adenomas of the parathyroids and pancreatic islets should be considered [5] There have appeared several reports in which primary hyperparathyroidism was simulated by thyrotoxicosis [40e] Hypercalcemia was encountered in these instances along with the associated anorexia nausea, vomiting, severe myasthenia mental changes, demineralization, and abdominal pain All these manifestations subsided when a euthyroid state was induced by means of antithyroid medication It is also pointed out that cases of simultaneous hyperfunction involving the thyroid and parathyroid glands have been recorded [40f, 6]

It has been estimated that up to 15 per cent of parathyroid adenomas are found in various ectopic sites of the neck and the mediastinum Accordingly, if the surgeon is unable to find a parathyroid tumor after a careful search throughout all areas in the neck in a bloodless field, the mediastinum should be explored at the same operation [69b]

Several instances of pancreatitis are on record in association with hyperparathyroidism so that the former disorder might actually alert the clinician to the presence of this endocrinopathy [73a] It is assumed that the hypercalcemia favors the deposition of pancreatic calculi which in turn result in ductal obstruction and pancreatitis Under such circumstances the serum calcium levels may prove to be unreliable both diagnostically and prognostically Furthermore the initial attack of acute pancreatitis has been observed on several occasions following the removal of a parathyroid adenoma [69a, 3b] There may be occasional instances in which osteomalacia and parathyroid hyperplasia are the aftermaths of pancreatic insufficiency with its impaired absorption of calcium and vitamin D [73c]

It is apparent that peptic ulcer is very common in the general population, and that several instances of the association of hyperparathyroidism with ulcer may have been due to either the milk alkali syndrome (Burnett) (p 406) or to its coincidence in patients with renal disease and secondary hyperparathyroidism Nevertheless, the observation concerning the increased frequency of this complication in the primary form of the disease is supported by significant experimental and statistical evidence (15 per cent in Howard's series) [74] In individual cases however, it may be impossible to distinguish the milk alkali syndrome from an occult hyperparathyroidism, short of pathologic study [75]

If a given case does not present one or several of the classic features, one should remember that in this disease in particular there is an exception to every rule This tenet was pointed out above with reference to the wide variability of the biochemical studies It is emphasized that no more

than half of these patients have roentgen evidence of bone disease and that renal disease is actually more common. An interesting subperiosteal resorption of bone occurs (most often along the margins of the phalanges of the hands), giving the bone beneath the periosteum a peculiar lacelike appearance.[76] Although this reaction is also noted in renal osteodystrophy, it has not been seen in the other metabolic bone disorders, such as osteoporosis and hypervitaminosis D. A roentgen sign that may be encountered in early clinical hyperparathyroidism and which is not seen in the other hypercalcemic states consists in the loss of calcium from the distal end of the clavicle.

Calcinosis cutis over pressure points (especially on the arms) with the formation of single or multiple hard nodules and plaques may make its appearance in this disease. It is of interest to note that this extensive subcutaneous calcification is actually unusual in hyperparathyroidism, and that it is more prone to occur in hypoparathyroidism. Several reports have described instances of parathyroid adenomas or carcinomas in which extensive calcinosis was a major presenting feature. On occasion, this would be manifested by a striking calcification of the vessels along with signs and symptoms of arterial insufficiency and even gangrene of the extremities.[69a, 77]

The changes in the gums in hyperparathyroidism are depicted in Figure 62 (Atlas page 39).

Osteoporosis, particularly in a male patient, should alert the physician not only to hyperparathyroidism but also to an underlying hyperthyroidism, pituitary hyperfunction, adrenocortical hyperfunction, myeloma, and sprue.[78] There may be no evidence of any associated tissue atrophy in the presence of severe osteoporosis. The finding of normal values for the serum phosphorus and serum alkaline phosphatase usually tends to exclude osteomalacia and hyperparathyroidism, whether primary or of renal origin. Some difficulty may be encountered in the case of osteoporosis due to myeloma since the serum alkaline phosphatase is rarely elevated in this disease. It is of added interest (but confusing diagnostically) that several cases of hyperparathyroidism have been reported in which the Bence-Jones protein could be detected in the urine.[79a] While the occasional elderly woman with mild postmenopausal osteoporosis may exhibit punch tenderness over the vertebrae, most patients who demonstrate considerable discomfort to this maneuver have serious underlying disease. (The subjects of postmenopausal osteoporosis and the osteoporosis associated with primary ovarian agenesis are further considered on pages 34 and 36 of this chapter, respectively.)

The "codfish" pattern of the osteoporotic spine is usually not due to true fractures, but to the expansion of the elastic intervertebral disc into the adjacent soft vertebral plates. Bartter has set forth the following radiologic features that have proved of great value in distinguishing osteoporosis from the other metabolic bone diseases: (1) the finding of radiolucency of the spine and pelvis in the presence of a normal skull (an abnormal skull strongly suggests another disorder), (2) a normal lamina dura about the teeth (its absence, even when there is considerable local dental decay, suggests osteomalacia, osteitis fibrosa, or some other metabolic

disease of bone), (3) the presence of vertically arranged "columns" within the vertebral bodies, (4) in the patient in whom the epiphyses have not yet closed, osteoporosis has no effect on the epiphyseal lines, in contrast to the definite changes observed in rickets and in renal hyperparathyroidism, and (5) the absence of bilateral, incomplete fractures that characterize osteomalacia, and of bone cysts and subperiosteal bone resorption that are found in hyperparathyroidism [78b] There are certain misgivings inherent in making the diagnosis of a postmenopausal osteoporosis solely on the basis of x rays of the spine If this caution is not heeded, some other existing disorder that affects the rest of the skeleton (such as Gaucher's disease) might be overlooked [290]

Although the osseous metastases from an underlying prostatic carcinoma are predominantly osteoblastic, there are instances in which the lesions are completely osteolytic This phenomenon is most apt to occur in the presence of a completely undifferentiated tumor [9b] In this regard, it has been shown that the acid phosphatase (and even the alkaline phosphatase and the prostatic phosphatase) can be normalized by orchiectomy and estrogenic therapy, or it may never have been elevated because of the inability of such poorly differentiated prostatic malignancies to function in the usual biologic manner The greater sensitivity of the "prostatic" serum acid phosphatase as compared with the total serum acid phosphatase in the diagnosis of metastatic prostatic malignancy is becoming increasingly appreciated (p 690) [79c]

Osteoporosis should be distinguished from *osteomalacia* ("adult rickets' due to improper calcification of the bony matrix) The latter can occur with or without tetany, hypocalcemia, or the pseudofractures resulting from the pressure of the surrounding vessels on the softened bone [80] Osteomalacia may be due to sprue and other chronic disorders which impair the absorption of the fat-soluble vitamins, to excessive calciuria in renal tubular acidosis or to osteitis fibrosa cystica following parathyroidectomy It is stressed that nontropical idiopathic steatorrhea often exists with but minimal gastrointestinal symptoms In such instances, severe skeletal pain (usually involving the back or the lower extremities), stiffness, weakness, and osteomalacia are apt to be the presenting manifestations [151] The finding of a normal serum alkaline phosphatase level in the presence of extensive bone disease usually definitely differentiates osteoporosis from both osteomalacia and osteitis fibrosa cystica (in which great elevations are expected)

Hypophosphatasia is a rare genetically determined inborn error of metabolism characterized by the following three features (1) low serum phosphatase activity reflecting a true decrease in the concentration of this enzyme throughout the body (2) marked skeletal abnormalities due to defective calcification in preosseous cartilage and in recently deposited bone matrix, with a complete disappearance of the zone of provisional calcification in very young children and a premature loss of the primary teeth, and (3) increased urinary excretion of phosphorylethanolamine [81] There have been approximately 35 typical cases of this disorder recorded in recent years, several diagnosed in adults Neuhauser and his colleagues have presented a comprehensive clinical pathologic radiographic account

of hypophosphatasia in a review of the cases collected both from their personal experience and the literature.[15a]

HYPOPARATHYROIDISM, PSEUDOHYPOPARATHYROIDISM, AND TETANY

Post thyroidectomy hypoparathyroidism must always be diligently searched for in the form of paresthesias, ocular spasms, and the "stiffness" due to mild tetany. This is far from an academic consideration since if it is not promptly recognized and treated, cataracts can develop in as early a period as two to six months.

Idiopathic hypoparathyroidism is a distinctly rare disorder in adults. It usually either remains undiagnosed or is recognized only after many years, during which time irreversible complications have set in. This sequence can be appreciated better in view of the mild, varied, and vague signs and symptoms, including fatigue, muscular weakness, gastrointestinal irritability, mental dullness, neurotic behavior, palpitations, paresthesias, and latent tetany.[81] (One recent case report cites the instance of a sixty-seven year old attorney who had been suffering from grand mal-like seizures since the age of forty six, along with depression, nervousness and weakness; once corrective therapy with dihydrotachysterol and calcium were instituted, he was able to resume an active law practice in his seventies.)[81d] It may also present itself in adults as dementia and epileptiform seizures.[81b] The significant cutaneous features of hypoparathyroidism consist of dry, scaly and pigmented skin, scanty hair and transverse grooving of the nails. This diagnosis can be most confidently made when the hypocalcemia is associated with a high serum inorganic phosphorus, the absence of severe renal insufficiency, the absence of chronic diarrhea, and no radiographic evidence of rickets or osteomalacia.

The appearance of the nails in hypoparathyroidism is depicted in Figure 30 (Atlas page 19).

In patients with concomitant arteriosclerotic or other forms of heart disease, the manifestations of hypoparathyroidism might be readily attributed to cardiac asthma.[81c] Prolongation of the JT or ST interval serves as a valuable electrocardiographic clue to the possible presence of hypocalcemia and is a reversible aberration. In this regard, the association of hypocalcemia with even moderate elevations in the serum potassium may be characterized by cardiac arrest or defects of intraventricular conduction resembling a bundle-branch block.

The association of the idiopathic form of hypoparathyroidism with mental retardation, calcification of the basal ganglia, hypoadrenocorticism, and moniliasis during the first decade similarly emphasizes the need for early diagnosis and treatment.[12, 81] The clinician should be cognizant of the fact that these patients are often more susceptible to hypercalcemia and intoxication by vitamin D than normal individuals, particularly when the calcium intake has been greatly increased.[8] This problem is further discussed under Group XIII (p. 403).

The still somewhat controversial entity of *pseudohypoparathyroidism* is presumably due to a "target organ defect." A typical build (round face,

short and stocky stature), changes in the shape of the abnormally short metacarpal and metatarsal bones, and calcification or actual ossification in the skin, muscles, tendons basal ganglia and lens are found, in addition to hypocalcemia and tetanic episodes [83] [84] One might suspect the meta carpal anomaly by the deficient or recessed knuckle prominence observed with the clenched fist, particularly over metacarpals IV and V Convul sions are common, resulting in the frequent misdiagnosis of epilepsy The inability of these patients to respond to potent parathyroid hormone can be demonstrated by the Ellsworth Howard test (p 726) They do respond, however, to dihydrotachysterol and vitamin D Some of the above features may be absent in certain "formes frustes" of this disorder The nosologically awkward term "*pseudo pseudohypoparathyroidism*" has been applied to instances where all the components are present except for the low serum calcium and the elevated phosphorus [85]

The manifestations of pseudohypoparathyroidism in the hands are depicted in Figure 61 (Atlas page 39)

Two considerations arise recurrently in the evaluation of *unexplained tetany*, namely, the presence of normocalcemic levels in some of these pa tients, and the difficulty in determining the amount of ionized blood cal cium Several reports have emphasized the role of estrone in such instances This observation is supported clinically by the increased tendency of the c attacks to occur in the premenstrual period and in the latter half of preg nancy, and their abolition by x-ray castration when no response to dihydrotachysterol (A T 10) was forthcoming [86]

THE ADRENOCORTICAL HYPERFUNCTION SYNDROMES

The classic *spectrum of adrenocortical hyperactivity* ranges from the Cushing syndrome with its associated manifestations of protein depletion, through the problem of hirsutism with obesity to the syndromes of viril izing pseudohermaphroditism and precociousness in children wherein the protein anabolic effects are so prominent [87] [88] [89] The clinician should con sider this not so rare diagnosis when confronted with such everyday problems as hypertension diabetes mellitus polycythemia, and osteoporosis Premature calcification of the abdominal aorta and its branches, and cal cification of the periarticular soft tissues of the hands—not unlike that seen in hyperparathyroidism or vitamin D intoxication—may be encoun tered in Cushing s disease [90] I recently had occasion to see a forty year old woman with the typical Cushing syndrome who had been treated for a large chronic leg ulcer over a period of nine months It was only when the skin would not hold the sutures that a systemic cau e was suspected (Resection of a cortical adenoma effected a complete cure)

The cutaneous manifestations of the Cushing syndrome and adrenal virilism are depicted in Figures 58 and 59 (Atlas pages 37 and 38)

There have been ample patients with adrenocortical hyperfunction without the moon face, buffalo hump and obesity to indicate that these features are not diagnostic essentials "Incomplete" clinical adrenocortical hyperfunction is often manifested by weakness (due to the negative nitrogen balance), back pain mental symptoms hypertension, osteoporosis

striae (only of diagnostic significance if they are pigmented), a diabetic type glucose tolerance test, and eosinopenia [86] Attention is called to the fact that adrenal atrophy is much more readily recognized by the surgeon than is hypertrophy Consequently, if neither tumor nor atrophy of the gland is found at the operating table in a patient with unmistakable evidence of Cushing's syndrome, one is justified in removing 90 per cent of the first gland and all of the second adrenal

It should also be emphasized that there are many women who have hirsutism, obesity, irregular menses, hypertension, and diabetes mellitus, but in whom no presently known adrenal or other endocrine disorder can be detected This combination is often found to represent a familial trait A similar admonition applies to the diagnosis of the adrenogenital syndrome in males when based solely on early pubescence, gynecomastia, and impotence without testicular atrophy

The ability to make a fairly accurate preoperative pathologic diagnosis of hyperplasia, benign adenoma, or malignant tumor of the adrenal cortex by measuring the urinary steroids following corticotropin stimulation is truly a tribute to modern endocrinology [87-91] Although Cushing in 1932 initially implicated adenomas of the basophilic pituitary cells in the syndrome bearing his name this is distinctly uncommon Furthermore since hyperplasia and hyalinization of the basophil cells are seen in the pituitary following corticoid therapy, these so-called Crooke s cells are probably secondary to the hypercortisonism and cannot be considered to be of primary importance in the pathogenesis of this state [93] Nevertheless, the possibility of roentgen irradiation to the pituitary region should be seriously considered in certain patients with the Cushing syndrome in whom no adrenocortical tumor can be demonstrated (short of laparotomy) A marked to complete remission has been induced within three to six months in many of these instances by employing a relatively low total roentgen dose delivered at a high average daily increment [93b]

Another functioning adrenal cortical tumor—the existence of which has only very recently been appreciated—is the adenoma producing large amounts of the mineralocorticoid, aldosterone (previously referred to as electrocortin) consequently, the syndrome has been labeled *primary aldosteronism* [94] (Along with the osmoreceptors in the carotid arteries, aldosterone secretion appears to play a significant role in extracellular fluid electrolyte homeostasis There is apparently much less control over the secretion of aldosterone exerted by the pituitary and its adrenocorticotropic hormone than is the case with the other adrenal hormones This hormone concomitantly promotes sodium retention and potassium excretion)

Intermittent tetany paresthesias chronic severe muscular weakness polyuria, polydipsia and hypertension are described, but interestingly no edema or "cushingoid features (The absence of edema is probably attributable to the inability of the kidneys to respond to the hormones regulating fluid and electrolyte balance in the body in the presence of severe potassium depletion) Diabetes insipidus may be seriously considered until the absence of a therapeutic response to Pitressin is noted

Laboratory studies in this disorder reveal low blood potassium levels

high blood sodium levels, an alkalosis with an alkaline urine, normal urinary 17 ketosteroid levels, normal sodium excretion, a decreased Na/K ratio in the saliva and sweat, and the presence of very high titers of potassium and a sodium retaining substance in the urine The presently available assay methods for aldosterone are not totally satisfactory The presence of normal values in the urine does not necessarily exclude primary hyperaldosteronism, a fact that is more readily appreciated when one considers the cyclic changes in the activity of this disease (as also characteristically takes place in the Cushing syndrome and in hyperthyroidism) Conn has even suggested that a partial or complete adrenalectomy be performed for a possible aldosteroma in patients with profound and unexplained hypokalemic alkalosis [96a]

It is pointed out that this entity differs from those conditions in which a high urinary aldosterone titer is a secondary manifestation, as occurs in nephrosis heart failure, and cirrhosis In these states, this represents an effect not only of the underlying disease process, but also of treatment, particularly desalting procedures The significance of a chronic, low grade state of hyperaldosteronism in human hypertension and its bearing upon the abnormalities of sodium metabolism are as yet not fully appreciated

THE ANTERIOR PITUITARY HYPERFUNCTION SYNDROMES

Pituitary tumors are mentioned primarily to alert the reader to the problem of "*fugitive acromegaly*," wherein hypersecretion may occur in the early phases of a chromophobe tumor One should obtain films of the sella turcica along with accurate visual field studies in problem cases of hypertension, thyrotoxicosis diabetes mellitus, arthritis, amenorrhea, diminished sexual function in males, headache, and disturbances of vision [97] Comedones, coarse hypertrichosis, spoon nails, and pigmentation, freckling or coarsening of the skin frequently occur

In both man and animals, the clinical sequence associated with the gradual destruction of the pituitary gland usually consists first of hypogonadism, then of hypothyroidism and finally of hypoadrenalism [98c] This would imply that more pituitary influence is necessary to support the function of the gonads than that of the other two endocrine glands There are, of course, many well documented instances of selective failure of the thyroid and adrenals as a result of thyrotropin or corticotropin failure It must also be recognized that hypogonadism secondary to chromophobe tumors might represent the effect of the tumor's pressing on the hypothalamus rather than primary hypopituitarism

It is well to bear in mind that gigantism is more often encountered as as a concomitant feature of primary eunuchoidism rather than being due to an eosinophilic tumor or hyperplasia of the pituitary gland The effects of the secondary hyperadrenalism or hypothalamic irritation (mental changes, obesity) produced by the pituitary disturbance might initially impress the clinician Another subtle manner in which acromegaly can first manifest itself is by the "carpal tunnel syndrome" In this instance, a median nerve neuritis is produced by the enlarging bone, resulting in a partial thenar atrophy Pituitary tumors rarely cause Cushing's synodrome (p 29)

One should not be too hasty to attribute the decreased visual acuity in patients with pituitary tumors solely to the direct pressure effects of the neoplasm on the optic pathways. Severe pituitary myxedema may also be contributory. Instances are on record in which the administration of thyroid caused a disappearance of the bilateral hemianopsia in such circumstances after the patient had refused surgery and irradiation.[96d]

In a patient who suddenly loses his vision without obvious cause, it is also important to consider the possibility of acute hemorrhage into a pituitary tumor, even though the usual clinical signs of such a lesion may not have been previously manifest. This also poses one of the major complications of roentgen therapy directed to these tumors. Accurate plotting of the visual fields may help in establishing the diagnosis early, which is imperative not only to save the vision but also to prevent both undue pressure on the vital adjacent structures and an increase in intracranial pressure.[97c]

Albright and Hurxthal have emphasized that the fasting serum inorganic phosphorus is at present the only good and practical laboratory evidence of excessive growth hormone secretion (values above 4.5 mg. per 100 ml. after 18 years).[99] It is also one of the best available criteria for the gauging of adequate radiation therapy.[99b]

THE PITUITARY HYPOFUNCTION SYNDROMES

The anterior pituitary hypofunction syndromes will be discussed at somewhat greater length with particular reference to the entity known as Simmonds' disease and its subclassifications of Sheehan's syndrome, gonadal failure, pituitary Addison's disease, and pituitary myxedema. Emphasis has already been directed to the last two especially relative to the hazards of instituting treatment solely with thyroid hormone. The response of the target glands to the administration of the various tropic hormones of the pituitary (primarily thyrotropin and corticotropin) is of unique value in the diagnosis of the deficiency syndromes resulting from pituitary failure. Other laboratory observations common to most hypopituitary states include anemia, eosinophilia, a flat glucose tolerance curve, increased sensitivity to insulin, hypometabolism, and decreased excretion of both the 17-ketosteroids and 17-hydroxysteroids. I have not found the level of the blood cholesterol as helpful in the differentiation of primary myxedema from pituitary myxedema as the literature might lead one to expect.

The anterior pituitary may be damaged by vascular occlusion, granulomatous and xanthomatous lesions, inflammation, hemorrhage, and primary or metastatic suprasellar neoplasms. Panhypopituitarism has even resulted from the compression produced by a large intracranial aneurysm originating from the internal carotid artery.[96]

Cases are on record in which progressive visual failure, scotomata, and headaches were present for seventeen years or longer before a chromophobe tumor of the pituitary was suspected.[98a] Much of the delay in the onset of recognizable manifestations of this tumor can be explained by the following two facts: (1) the considerable expansion that is possible (since the pituitary normally occupies only about one-half the volume of the sella

high blood sodium levels, an alkalosis with an alkaline urine, normal urinary 17 ketosteroid levels, normal sodium excretion a decreased Na/K ratio in the saliva and sweat, and the presence of very high titers of potassium and a sodium retaining substance in the urine The presently available assay methods for aldosterone are not totally satisfactory The presence of normal values in the urine does not necessarily exclude primary hyperaldosteronism, a fact that is more readily appreciated when one considers the cyclic changes in the activity of this disease (as also characteristically takes place in the Cushing syndrome and in hyperthyroidism) Conn has even suggested that a partial or complete adrenalectomy be performed for a possible aldosteroma in patients with profound and unexplained hypokalemic alkalosis [94]

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The appearance of a true *diabetes insipidus* should similarly initiate a search not only for primary neoplasms, trauma, or vascular lesions affecting the hypothalamicodiencephalic area, but also for a familial background and a number of other systemic causes.[104-106] These include metastatic cancer, amyloidosis, the dyscollagenoses, leukemia, lymphoma, sarcoidosis, infection (tuberculosis, endocarditis), chronic encephalitis, and eosinophilic granulomatosis (the Hand Schüller Christian syndrome). The association of diabetes insipidus with both failure of growth and delayed puberty is suggestive of the Hand-Schüller Christian disease.

Any pathologic process or surgical procedure that destroys the posterior pituitary, its stalk or the hypothalamus might result in diabetes insipidus.[104b] • For example, diabetes insipidus has been associated with generalized osteosclerosis and periosteal proliferation involving the vertebrae and base of the skull.[104d] This complication is infrequently noted, however, since at least 85 per cent of the cells in the supraoptic nuclei must be destroyed before this syndrome occurs. On the other hand, as the tumor involves the anterior lobe of the pituitary, the diabetes insipidus may disappear.[106b]

In addition to the two types of diabetes, polyuria and polydipsia should alert the clinician to kidney disease, hypercalcemia, primary aldosteronism and functional disorders. *Nephrogenic diabetes insipidus* is transmitted as a recessive sex linked characteristic, the complete clinical picture being found only in males.[179e] It is not unlikely that the retarded mental development in these children is partly due to the recurrent or persistent hypernatremia. In contrast to the patient with true diabetes insipidus, there is no response to vasopressin (Pitressin) in these patients. While some of these individuals do reach adult life, there is little improvement that can be expected in the defective water reabsorption. The polyuria encountered in cases of unilateral renal hypertension has been confused with diabetes insipidus. It presumably stems from the increased amounts of renin and hypertensin released into the renal venous circulation.[107] A Pitressin-resistant polyuria can also accompany the nephropathy associated with potassium loss or depletion (p. 80).

If the total daily output of urine is less than 4 liters, diabetes insipidus is probably not present. The diagnosis of diabetes insipidus is most conclusively made by demonstrating hyperosmolarity of the serum associated with a dilute urine.[108] In the case of diabetes insipidus produced by metastatic cancer, large losses of urinary sodium may occur due to the normal response of aldosterone secretion.[109]

Thorn and his colleagues have clearly shown that the functional state of the neurohypophyseal-renal system can be readily evaluated in patients with polyuria by the serial intravenous administration of nicotine, hypertonic saline solution, and Pitressin under constant water loading conditions.[110] Under these influences—by means of which stimulation of the hypothalamic nuclei, the osmoreceptors, and the renal tubules are induced, respectively—the changes in the free water clearance serve as a convenient and reliable index of ADH activity.

It can be inferred that neurohypophyseal failure exists when no antidiuretic response is forthcoming to the administration of nicotine and hy

turcica), and (2) hypopituitarism does not usually manifest itself until the destruction of the gland is almost complete The wide range of possible visual abnormalities produced by pituitary tumors should be appreciated They may range from a homonymous hemianopsia to unilateral or bilateral blindness, due to the many manners in which the optic apparatus might be compressed There have been instances in which the gonadal function was primarily affected in the absence of impairment of either the vision or the adrenocortical or thyroidal function [98b] The demonstration of hypoglycemic unresponsiveness by the careful use of the intravenous insulin tolerance test has proved of value in diagnosing pituitary destruction in such situations (p 720) [98]

The skin of the patient with hypopituitarism may exhibit a number of changes These include a pale-yellow, smooth and thin appearance, freckling in the exposed areas, dystrophy of the nails, and alopecia over the vertex, lateral eyebrows, axillae and pubes The presence of axillary hair is consistent with recent panhypopituitarism, however, since it takes several months for the effect of the hormones that maintain its growth to wear off The reader need hardly be reminded of the fact that the so-called Frohlich s syndrome usually turns out to be delayed pubescence in boys associated with obesity, rather than pituitary or hypothalamic disorders

Postpartum necrosis of the anterior pituitary gland must be considered in *every* woman who complains of asthenia and persistent loss of sexual function, with or without weight loss, following a previous delivery which had been characterized by considerable hemorrhage and shock [100] Severe headache is also very common following infarction of the pituitary The repeated attacks of hypoglycemia which they experience pose a serious threat to these patients This condition is one of the most serious long term sequelae of obstetric complications and is by no means rare, as evidenced by the many postmortem cases and the many patients seen clinically by Sheehan over a four year period [101] It is truly a tragedy when such a patient is labeled psychoneurotic

The cutaneous manifestations of Sheehan's syndrome are depicted in Figure 57 (Atlas page 37)

The absence of urinary FSH in postmenopausal women or in younger women with hypothyroidism and amenorrhea makes the diagnosis of pituitary hypothyroidism almost a certainty (p 720) [102] (The determination of the urinary gonadotropin level provides a more rapid and direct indication of interference with the pituitary's secretory activity than does the estimation of the indirect effects of pituitary hypofunction on thyroidal, gonadal, and adrenal function) Several observers believe that partial postpartal insufficiency occurs much more frequently than the fully developed syndrome Temporary improvement becomes apparent in these instances during a subsequent pregnancy as a result of the physiologic hypertrophy of the pituitary remnants

The diagnosis of Falta s syndrome or *multiple glandular sclerosis* in which there is fibrosis and destruction involving the pituitary, adrenals, thyroid, and gonads, has occasionally been entertained in cases of panhypopituitarism Evidences of sarcoidosis, hemochromatosis, and amyloidosis should be carefully sought out before this diagnosis is made [103]

the case with asymptomatic and unrecognized vertebral fractures in the osteoporotic spines of the aged The prolonged latent interval (ten to twenty five years) can be comprehended more readily if one considers that a 30 per cent loss of the calcium in the spine (approximately 400 gm or 400,000 mg of calcium) must precede the x ray changes, and that the average loss of calcium by the climacteric patient is approximately 100 mg daily [118] The skull is rarely involved, however, in contrast to hyperparathyroidism Once the disorder reaches its fully developed stage, the serum calcium and phosphorus levels are normal, but the urinary excretion of these substances is low

OTHER OVARIAN SYNDROMES

Ovarian tumors occasionally manifest themselves by striking disease complexes *The Meigs Cass syndrome* of ovarian fibroma, ascites and pleural effusion (usually on the right side) is a most interesting entity [119] Another group of ovarian neoplasms which has proved to be very elusive is the so-called *Krukenberg tumor*, whether primary in the ovary or metastatic from the gastrointestinal tract This diagnosis should be entertained when the triad of persistent dyspepsia, anorexia with epigastric discomfort, and a firm adnexal tumor is found, particularly in women of reproductive age [120]

The functioning ovarian neoplasms producing either feminization (granulo a cell tumor, theca cell tumor) or masculinizing effects (arrhenoblastoma, adrenal rest tumor, Leydig cell tumor) are quite rare and will be mentioned but briefly [121] It should be appreciated that the initial effects in the latter disorders are basically those of "defeminization, as characterized by cessation of menstruation, sterility, and the general loss of feminine contour and skin texture The masculinizing effects then occur, consisting of hypertrophy of the clitoris, development of a masculine habitus, the husky voice, the beard, and the android body hair growth (p 529) The absence of an enlarged ovary does not necessarily rule out a functioning tumor of this organ since arrhenoblastomas may occur as small, benign nodules [121, 122]

Several comments are in order concerning the occasional problem of *precocious puberty* in the young female The finding of disks of glandular tissue in both breasts confirms its presence There is little doubt that most of these girls have either the cerebral or the constitutional type of precocity, even with ovulation taking place While feminizing mesenchymal tumors of the granulosa cell type may occur in very young females, thecomas rarely do and are limited primarily to the middle-aged and elderly patient

When a pelvic mass accompanies precocious puberty, another likely possibility is that of single or multiple follicle cysts of the ovary with luteinization The cystic changes may be unilateral or bilateral, and are independent at times of central stimulation The vaginal blood in these patients usually clots because of the noncyclically stimulated endometrium of the hyperplastic proliferative type It is pointed out that even when precocity of the cerebral or constitutional type is known to exist—

pertonic saline solution The diabetes insipidus-like syndrome resulting from primary destruction of the posterior pituitary (in spite of the preservation of hypothalamic neurosecretory function) is demonstrated by a normal response to small doses of nicotine, but the absence of the anticipated response to the saline infusion Finally, patients with psychogenic polydipsia often exhibit abnormal responses to nicotine, but normal responses to the saline solution Persistent unresponsiveness to large doses of nicotine in patients who are receiving cortisone is suggestive of hypothalamic damage The comparative renal responses to water and saline administration, water deprivation, nicotine, and antidiuretic hormone are reviewed in Part II (pp 721, 812, and 819)

THE MENOPAUSAL SYNDROMES

The menopause must obviously be considered as a contributing cause of the various metabolic, cardiovascular, genitourinary, and nervous conditions occurring in women of the appropriate age group[113] While it is true that most of the symptoms are related to the associated psychologic conflicts and, to a much lesser extent, the diminished estrogen production, the tendency to attribute *all* symptoms in this era of life to the menopause—both by physicians and by patients—may be tragic The hazards attendant upon the indiscriminate use of large doses of oral estrogens as an "all purpose female tonic" and of estrogenic skin creams are reviewed under Group XIII (p 405)

An occasional woman presents herself with a spontaneous *premature menopause* in the fourth or even the third decade, this often proves to be a familial trait It is always wise in these instances, however, to be sure that one is not dealing with adrenocortical insufficiency, hypopituitarism, the Cushing syndrome, hyperthyroidism, poor nutrition, or a severe anxiety state

It must also be borne in mind that *excessive uterine bleeding* may occasionally be the first manifestation of a blood dyscrasia (particularly pseudohemophilia, thrombocytopenic purpura and the other hemorrhagic states),[114] severe liver damage with hyperestrinism,[115] and other nonendocrinologic systemic disorders

Several interesting clinical entities have been noted during or after the menopause An unusual form of *muscular dystrophy*, consisting of a progressive weakness of the hip and shoulder girdle muscles, is described[116] A number of reports particularly from the Scandinavian countries, have indicated the higher incidence and mortality rates of *infectious hepatitis* in menopausal women[117] This has repeatedly been the author's experience in dealing with a number of these patients *Keratoderma climactericum* is an extensive hyperkeratosis involving the palms and soles It may be ameliorated by hormonal therapy An illustration of keratoderma climactericum appears in Figure 54 (Atlas page 34)

Postmenopausal *osteoporosis* usually occurs ten or more years after "the change" It should be considered when such a patient complains of persistent backache This diagnosis can be overlooked even by the roentgenologist if the density changes in the spine are slight, this may also be

from pituitary ovarian deficiency by the increased growth of sexual hair following estrogenic therapy, the hypoglycemic responsiveness, the associated congenital anomalies and the previously discussed increased levels of FSH in the urine Although cyclic administration of estrogen constitutes the treatment in these patients, this drug should *not* be administered until it is apparent that no further growth is occurring (since large doses of estrogen might result in the premature closure of the epiphyses) This therapy is positively indicated in later years however, to avoid the pain and deformity of the inevitable severe osteoporosis

It is of interest that several male patients with hypogonadism and associated multiple congenital defects have been reported[1 7] Furthermore, the definitive sex chromatin determinations have shown most of patients with gonadal dysgenesis to be actual genetic males

One revealing finding stemming from the current interest in the determination of chromosomal sex and male infertility has been the evolution of the belief that micro-orchidism with gynecomastia (*the Klinefelter syndrome*) probably represents a genetic defect in the sex chromosomes A study of the testicular tissue in the chromosomal positive patients with this disorder gives the impression that the gonads are probably modified ovaries[129] Instances of ovarian agenesis and the Klinefelter syndrome have also been found in families afflicted with amyotonia congenita (Oppenheim s disease) and infantile cataracts[1 7 1 9]

The Klinefelter syndrome is depicted in Figure 60 (Atlas page 38)

including that associated with Albright's syndrome—a regression has on occasion followed the *removal of a concomitant luteinized ovarian cyst*[1.b]

More common and important than these aforementioned disorders in a consideration of hirsutism and amenorrhea is the *Stein-Leventhal syndrome* due to polycystic ovaries with a thick ovarian capsule While the hirsutism in itself will *not* be affected, a wedge resection might cure the patient if the 17 ketosteroid and FSH levels are normal, if consistent anovulatory function is present, and if adrenal suppression by cortisone does not induce ovulation and regular menses[1.3] Clinicians and gynecologists should note that 17 of 45 patients with the Stein Leventhal syndrome studied at the Mayo Clinic were found to have an associated endometrial carcinoma[123c]

In the presence of frank virilism with normal 17 ketosteroid levels and excessive bleeding, alternating with periods of amenorrhea, the entity of *ovarian hyperthecosis* should be considered[1.4a] There have been instances in which the ovaries have shown an overlapping between the pathologic picture of the Stein Leventhal syndrome and hyperthecosis in patients with menstrual disturbances progressive hirsutism, and a profound rapid gain in weight[1.4b] (The term hyperthecosis refers to the luteinization of the ovarian stroma whether or not luteinized follicle cysts are also present) One interesting patient with hyperthecosis is on record whose mother also had hyperthecosis[1.4b]

The cutaneous manifestations of luteinization of the ovaries are depicted in Figure 99 (Atlas page 64)

The ovaries by culdoscopy (see Section V of Part II) may present characteristic appearances in the Stein Leventhal syndrome, hyperthecosis, arrhenoblastoma, and the rare hilar cell tumors[1.5] In experienced hands this technique is particularly advantageous in the presence of marked obesity which tends to render palpation of the ovaries unsatisfactory If amenorrhea, hirsutism and obesity are associated with normally appearing ovaries, adrenal abnormality must be suspected

The remarkable association of multiple congenital defects and *primary ovarian agenesis or arrest* has been pointed out by Turner, with whose name the syndrome has already become identified (The term gonadal dysgenesis is generally being employed now and is synonymous with Turner's syndrome ovarian agenesis primary ovarian insufficiency with decreased stature syndrome of rudimentary ovaries, and the Bonnevie-Ullrich syndrome) The majority of these women are seen in their third or fourth decades They exhibit a short stature (due to the delayed epiphyseal development) underdevelopment of the genitalia and breasts, absence of the axillary and pubic hair, and osteoporosis—but with no impairment in their sense of well being and *no* hot flashes Among the numerous congenital anomalies reported in these cases, webbing and shortening of the neck, cubitus valgus various ocular abnormalities, a shield chest, and coarctation of the aorta have been encountered most commonly[1.6]

The cutaneous manifestations of ovarian agenesis are depicted in Figure 63 (Atlas page 40)

In addition to the castrate vaginal smear and the minimal excretion of urinary 17 ketosteroids, the nature of this disorder can be differentiated

THE POISONINGS

Bromides Salicylates DDT Lead The solvents
The alcohols Mercury Arsenic

DIABETES MELLITUS

OTHER "ERRORS OF METABOLISM"

Gout
Ochronosis
Galactosemia

THE GLYCOGEN-STORAGE DISEASES

THE DISORDERS OF LIPID METABOLISM

Xanthomatosis
Essential Familial Hypercholesterolemia
Essential Hyperlipemia
Lipoid Proteinosis
Gaucher's Disease

THE SPECIFIC ELECTROLYTE DEPLETIONS

Potassium Sodium Chloride Magnesium

THE SPECIFIC ELECTROLYTE EXCESSES

Sodium Chloride Potassium Ammonium Calcium
Magnesium

UNDER the general heading of Metabolic Disorders the author has included those conditions which interfere in some manner with the normal biochemical processes of the body or that result from such metabolic derangements It is apparent that many of the diseases listed elsewhere could also be cited here and that many others have been omitted, such as the more unusual inborn errors of metabolism A comprehensive summary of the diagnostic approaches to many of the entities in this chapter may be found in Part II under Section II (Blood Chemistries), Section III (Renal Function Urinalysis) and Section VII (Studies of Gastrointestinal Function)

MALNUTRITION

In every patient with weight loss and fatigue for whom no diagnosis can be made specific inquiry into the intake of calories proteins, minerals, and vitamins would seem to be a *sine qua non* Yet the author has encountered patients who have been subjected to numerous diagnostic procedures because of unexplained weight loss and in whom a *lowered food intake* has proved to be the entire explanation To cite but one example is the instance of the otherwise healthy young man who has been troubled by a significant weight loss after returning from either school or the military service to an environment where fewer calories are served and to an occupation requiring less strenuous activity Particularly in the practice of geriatrics, it is very important to be constantly aware of the fact that the

GROUP II

Metabolic Disorders

Malnutrition

Lowered food intake Excessive loss of nutrients Increased requirements Kwashiorkor Unexplained weight loss The avitaminoses (beriberi, scurvy, pellagra, and their variants)

Obesity

Secondary cardiac hematopoietic, menstrual, and hepatic derangements

The Malabsorption Syndromes

Steatorrhea ((Primary Secondary)

Intestinal Lipodystrophy

Chronic Pancreatitis

Fibrocystic Disease of the Pancreas

Regional Enteritis

Ulcerative Colitis

Chronic Renal Disease

Uremia The tubular dysfunction syndromes Renal osteodystrophy The nephrogenic electrolyte-losing syndromes The potentially reversible types of renal insufficiency The nephrotic syndrome Unrecognized hydronephrosis The unrecognized decompensated urinary bladder

The Lignac Fanconi Disease

Renal aminoaciduria

Systemic Amyloidosis

Primary Secondary

Hemochromatosis

Primary Secondary Therapeutic

Porphyria

Acute Chronic Precipitating causes

Allergy

Serum sickness The Loffler syndrome

if the patient is to have any hope of surgical help *Hypernephroma* and *retroperitoneal lymphoma* are also often first apparent clinically by unexplained weight loss and malaise Another debilitating condition that is infrequently considered is the result of the previous performance of an *inadvertent gastroileostomy*[133] Since most gastroenterologists and surgeons have had experience with this problem, it is by no means a rarity When diarrhea and weight loss persist after a subtotal gastric resection, and the possibility of a gastroileostomy exists, the demonstration of a flat curve in an oral glucose tolerance test might be diagnostic[133b] The similarity of the clinical picture produced by extreme degrees of malnutrition to that following destruction of the anterior lobe of the pituitary gland may result in considerable diagnostic confusion This *functional hypopituitarism* can be differentiated from organic hypopituitarism only by its reversibility with refeeding and by the absence of an adequate and sustained response to specific endocrine therapy[134]

Nutritionists have shown that there has been a significant increase in the fraction of the average diet made up of "empty calorie" foods in the form of sugars, cooking fats and highly refined foods (as white flour products)—most notably at the expense of calcium, vitamin A, and vitamin C It might even be conclusively demonstrated at some future date that certain 'degenerative diseases, such as atherosclerosis osteoarthritis, senility and diabetes mellitus, actually result in a large measure from the chronic biochemical insults to the body incurred by a poorly balanced diet For example, striking evidence is already on hand to demonstrate that potassium (which is largely discarded in the water used to boil food) exerts a definite protecting effect against the cardiovascular and renal damage produced by chronic sodium chloride ingestion[132]

The significance of deficiencies and excesses of the oligoelements, such as copper cobalt and magnesium are cited elsewhere (pp 67, 100, and 385) This promises to be a fertile area for clinical discovery, as is already evidenced by the enhanced interest in the serum metalloenzymes In the case of zinc, for instance the serum levels are reduced in cirrhosis and fluctuate with the course of the disease Furthermore, some of the zinc enzymes (the glutamic, lactic alcohol and malic dehydrogenases) are already being widely appreciated as valuable adjuvants in the diagnosis of acute myocardial infarction cerebral infarction and liver disease[135]

It is most important to dissociate a lowered nutriture from 'normal' weight Such an orientation is imperative if one is to anticipate, recognize and treat such *avitaminoses* as beri beri pellagra, and scurvy in their earlier atypical phases and before serious pathologic changes have already occurred This is a particularly vital consideration in chronic alcoholics and when severely restricted diets are prescribed both in obesity and in other conditions (e g , the rice diet and the Sippy regimen) One of the axioms of replacement vitamin therapy is that deficiencies are usually multiple and that syndromes resulting from the isolated depletion of just one of these substances are unusual Occasional well documented reports of specific vitamin deficiency syndromes are reported For example, the case of an adult male with an acquired hypochromic anemia, which was refractory to all of the known hematopoietic agents and in whom a complete remission

vitamins and other "tonics" which are routinely prescribed in order to stimulate appetite are totally ineffective if the patient's diet does not contain sufficient calories.[130] The numerous subtle manifestations of malnutrition in the elderly include profound mental and psychiatric aberrations, hepatomegaly, muscular atrophy, vague gastrointestinal symptoms and anorexia.[130c]

The *causes of malnutrition* can be readily subdivided into inadequate diet, loss of appetite, inability or unwillingness to eat, impaired absorption, excessive loss of nutrients, liver disease, and increased requirements (hyperthyroidism, fever, growth, pregnancy, congestive failure). The contribution of malnutrition to obscure illness and the inability of the organism to withstand infections and physical stress, both directly and indirectly, is considerable and must never be ignored or minimized. For instance, the problems attendant upon unsupervised weight reduction diets—in which many overweight individuals freely engage according to the current fashion—continually confronts physicians. This was recently re-emphasized by the inability of obese patients to maintain nitrogen balance on a low protein regimen then in vogue, popularly mislabeled as the "Rockefeller diet."[131a] The clinician might not be aware of this significant background of compulsive dieting with its subtle effects on the body's economy unless it is directly sought out.

Fortunately, few physicians in the United States have encountered *kwashiorkor*, a serious system disorder in children stemming from severe protein deficiency.[131b] The weight loss and mental apathy are accompanied by a generalized edema, hepatomegaly, diarrhea, and a unique dermatosis that differs from pellagra. (The term itself stems from the native designation for "red boy," since the hair may change to a red hue.) The hyperkeratosis and hyperpigmented areas are most prone to involve the groin, the axilla, and the chest wall. It is pointed out that lightness or redness of the hair is not a manifestation specifically associated with kwashiorkor, since it can take place in ulcerative colitis and other disorders associated with malnutrition.[131c]

Clinicians must never lose sight of the fact that protein malnutrition *is far more prevalent throughout the world than overt vitamin deficiency* or starvation. In many instances, the children afflicted with kwashiorkor have also been *subjected to the various infections and infestations which* produce anorexia, vomiting, and diarrhea that further interfere with the proper intake and absorption of their already limited food. Edema is common, but hardly ever as severe as in the case of nephrosis or beri beri. Ascites tends to be uncommon. *It should be stressed that vitamin therapy in high dosage—whether the vitamins are given singly or combined—is of* little value in the absence of protein (or possibly certain specific amino acids).

There are several entities in addition to those heretofore cited which may result in *unexplained weight loss*. One of the most characteristic features of *cancer affecting the body or tail of the pancreas* is the concomitant profound and rapid weight loss. When associated with a relatively normal blood count and the presence of abdominal or back pain *that is relieved* by either sitting up or bending over, this diagnosis *must* be entertained

other vitamin deficiencies[142] Pathologically, there is an invariable involvement of the same periventricular hypothalamic and thalamic regions, most notably in the mammillary bodies[14a] While severe chronic alcoholism is the background in well over 90 per cent of cases with the latter syndrome, it has been observed in nonalcoholic patients suffering from prolonged mal nutrition as a result of gastrointestinal cancer The importance of not mistaking the Wernicke syndrome for hepatic coma will be again emphasized (p 97)[156] While overt signs of congestive failure are infrequently noted in Wernicke s syndrome, a number of these individuals do demonstrate a state of peripheral vasodilatation (as characterized by a tachycardia, elevated cardiac output, low peripheral resistance, and postural hypotension) which is qualitatively similar to that noted in *beri beri*[149]

3 *Pellagra* is occasionally unrecognized in well to-do food faddists It may appear in the form of vague gastrointestinal symptoms or of paranoid behavior with mania and delusions of parasitosis[140] The cutaneous changes are often not apparent if the individual has had little exposure to sunlight Smith has cited the case of an elderly woman who developed probable pellagra after a thirty day course of chlortetracycline The cutaneous mani festations of pellagra are depicted in Figure 46 (Atlas page 28)

4 *Scurvy* has been observed in ulcer patients who have adhered to a strict Sippy alkali regimen without receiving supplementary ascorbic acid Inquiry into the administration of an antiscorbutic preparation is unfor tunately still necessary when confronted with a child below the age of two years who evidences tenderness of the legs, pseudoparalysis, irritability, and bleeding phenomena[141] The perifolliculitis and hemorrhagic skin manifestations encountered in adults are infrequently noted in infantile scurvy[141b] The cutaneous manifestations of adult scurvy are depicted in Figure 48 (Atlas page 30)

5 In addition to the neonatal period and the administration of drugs of the dicoumarin series symptomatic bleeding due to *vitamin K deficiency* may occur in obstructive jaundice, severe liver damage, intestinal fistulas, the malabsorption syndromes[153] and following prolonged oral therapy with the broad spectrum antibiotics or streptomycin

6 Clinicians and radiologists should be familiar with the entity of *vitamin D resistant rickets* (refractory rickets) This peculiar form of late rickets is characterized by dwarfism, severe deformities persistent hypophosphatemia and a good therapeutic response to very large doses of vitamin D[143] An attempt should be made to distinguish this condition—which is not associated with recognizable visceral disease—from renal rick ets, chondrodystrophy, osteogenesis imperfecta, poor absorption of vitamin D (as in pancreatic hepatic, or intestinal insufficiency) and hyperparathyroidism because of the potential dangers associated with therapeutic vitamin D excess In the presence of vitamin D resistant rickets and osteomalacia there are three different forms of renal tubular dysfunction (usu ally not strictly limited to either the proximal or distal parts of the tubular system) that might also be considered These consist of 'phosphate dia betes ' the Lignac-Fanconi syndrome and hyperchloremic tubular acidosis due to renal abnormality or to prolonged therapy with either Diamox or the acidifying salts[196] (See pages 52 and 57) On the basis of studies of

could be repeatedly induced by parenteral pyridoxine, has recently been described by Harris[136] The patient's symptoms appeared to be referable solely to the severe anemia, for which numerous transfusions were required prior to this unique observation

With the continuing introduction of *biologic competitors* into the realm of therapeutics, unanticipated deficiency syndromes will inevitably occur An example of this can be found in the pellagra and peripheral neuropathy due to vitamin B_6 (pyridoxine) deficiency that occurs in tuberculous patients being treated with large doses of isoniazid[137] Similarly, scurvy following therapy with the folic acid analogs is explained by the possible antagonistic action of aminopterin on vitamin C metabolism[138a] The administration of EDTA as a chelating agent has been followed by mucocutaneous lesions simulating those seen in the vitamin B deficiencies[138b] Profound losses of zinc and other minerals in the urine have also taken place with this type of therapy

It is necessary to bear in mind the cutaneous dermadromes of the avitaminoses A B, and C when variously confronted with a follicular hyperkeratosis, dry, scaling and pruritic skin lesions glossitis, seborrheic dermatitis, cheilosis, perifollicular hemorrhages, ecchymoses, and dry lusterless hair in patients whose diets have been inadequate On the other hand one must be very cautious in attributing such physical signs as thickening of the conjunctivae, keratosis pilaris (commonly confused with hyperkeratosis follicularis in children under twelve years of age), "corneal vascularization" and the cheilitis associated with the absence of teeth, to specific vitamin deficiency syndromes A certain degree of skepticism is also in order whenever a particular vitamin deficiency is offered as the explanation for various minor conditions in individuals consuming reasonably adequate diets There is little doubt that xerophthalmia, acneform eruptions, follicular keratosis, and ichthyosis may on occasion result from vitamin A deficiency, particularly in the presence of severe chronic liver disease, hypermetabolism, and the malabsorption syndromes Serious intoxication can be induced by the excessive administration of this vitamin over prolonged periods, however, when taken solely for a mild acne or a dry, harsh skin As noted later in this chapter and under the section on iatrogenic diseases, a similar consideration applies to massive niacin and vitamin D therapy (pp 96 and 403)

The following brief listing of significant observations relative to the diagnosis of several specific vitamin deficiency syndromes supplements the previous commentary

1 A *thiamine deficiency syndrome* mimicking thrombophlebitis is not infrequently encountered in postoperative and postpartum patients[139] Paresthesias, burning feet, mental changes, and other subtle neuritic features of combined thiamine-vitamin B complex deficiencies should not be overlooked in these and other situations

2 It is quite probable that both *the Wernicke syndrome* (ophthalmoplegia, ataxia, confusional mental state with or without a peripheral neuritis) and *the Korsakoff syndrome* (memory impairment, temporal disorientation, confabulation, with or without a peripheral neuritis) represent different clinical expressions of the same disorder namely thiamine and

of intestinal "absorption" Furthermore this term itself is defined differently by various authorities Both the vitamin A and the glucose tolerance curves have frequently proved to be quite unreliable The d xylose absorption test appears to be somewhat more advantageous (p 757) It is becoming increasingly appreciated however, that the plasma concentration of carotene is probably the best and simplest screening test we have *against* steatorrhea—particularly in its differentiation from functional diarrhea—since levels exceeding 70 micrograms per 100 ml are rarely found in the former state (p 685) [15]

Volwiler has set forth the following useful classification of the steatorrheas, based upon the principal biochemical and physical processes that are involved in the digestion and absorption of fat [15b]

A Inadequate mixing of food with bile salts, lipase
  1 Pyloroplasty
  2 Subtotal gastrectomy
  3 Total gastrectomy
B Inadequate lipolysis—lack of lipase
  1 Pancreatic insufficiency
    Congenital cystic fibrosis of pancreas
    Chronic pancreatitis
    Cancer of pancreas or ampulla
    Pancreatic fistula
    Protein deficiency
C Inadequate emulsification of fat—lack of bile salts
  1 Obstructive jaundice
  2 Severe liver disease
D Primary absorptive defect of small bowel
  1 Inadequate length of normal surface
    Surgical resection
    Internal fistula
  2 Obstruction of mesenteric lymphatics
    Lymphoma
    Carcinoma
    Whipple s disease
  3 Inadequate absorbing surface due to extensive mucosal disease
    Inflammatory—tuberculosis regional enteritis
    Neoplastic
    Amyloid infiltration
    Scleroderma
  4 Biochemical dysfunction of mucosal cells
    Celiac disease
    Sprue
    Severe starvation
    Transient dysfunction associated with intestinal infections
  5 Malabsorption associated with blind loops diverticula strictures

Severe absorption defects resulting in "intestinal invalidism" are to be expected in patients previously subjected to *extensive resections of the small intestine* particularly when performed for jejunoileitis or acute mesenteric

pedigrees involving as many as five generations, it has been postulated that some instances of vitamin D resistant rickets might be the result of a single dominant autosomal gene of variable expressiveness[143b]

OBESITY

Profound obesity can also result in serious pathologic changes and obscure illness, particularly when the gain in weight has been relatively rapid Symptomatic fatty infiltration of divers organs may be induced, most notably in the heart and in the liver[144] The author has recently reviewed the problem of adiposity of the heart as a cause of unexplained cardiac enlargement, heart failure, and conduction disturbances[145] Significant statistical proof has been gathered to verify the frequent association of obesity and manifold menstrual disturbances[146] Hyperinsulinism (organic or functional) hypothalamic disorders, the Cushing syndrome, *hypogonadism, and hypothyroidism are bona fide (but infrequent) causes* of obesity

It is not generally appreciated that falsely high blood pressure readings are often obtained in individuals with obese upper arms[147] In these very obese patients, determination of the radial artery pressure by either the auscultatory method or by palpation is more accurate

Varying degrees of arterial hypoxia with an associated polycythemia have been observed and carefully studied in patients with marked obesity who exhibited no evidence of concomitant cardiac disease, primary lung disease, or abnormal vascular communications This complication can be explained by the decreased tidal volume, resulting in alveolar hypoventilation, and subsequently leading to increased venous admixture, hypoxia, polycythemia, and even pulmonary hypertension with right heart failure[148 150] There is neither a splenomegaly nor an increase in immature cells white blood cells or platelets in the peripheral blood Weight reduction in itself has often proved curative The predisposition of the obese to decompression sickness will be considered in a later chapter (p 218)

THE MALABSORPTION SYNDROMES

The present discussion will deal chiefly with those malabsorption syndromes wherein broad groups of nutritional substances are involved rather than such specific malabsorptive defects as pernicious anemia and vitamin D resistant osteomalacia

STEATORRHEA

Since most of the standard medical texts cover the differential diagnosis of chronic diarrhea and the malabsorption diseases adequately only a few interesting aspects of this subject will be discussed here First several comments are in order concerning certain controversial aspects of the procedures employed in studying the malabsorption syndromes that may not be apparent in Section VII of Part II There are as yet no universally accepted criteria for even the normal variations in many aspects

necessarily indicative of diminishing fat and nitrogen losses Furthermore, it is again stressed that diarrhea need not be an essential feature of the steatorrheic syndrome

Symptomatic sprue secondary to lymphoma, amyloidosis, the dyscollagenoses, Whipple's disease, and tuberculosis must be kept in mind, particularly when no therapeutic response is forthcoming[155] Malignant carcinoid tumors of the gastrointestinal tract, regional enteritis, generalized intestinal polyposis, adrenocortical insufficiency, the mesenteric lymphadenopathy in Letterer Siwe disease[157c] and the enterocolitis in hypogammaglobulinemia can also produce sprue-like syndromes Severe steatorrhea may be encountered in long standing diabetics who demonstrate altered gastrointestinal motility because of the complicating diabetic neuropathy[159] Evidence of external pancreatic insufficiency or nontropical sprue is usually lacking in these instances The author has occasionally encountered patients who are concerned about a possible pathologic basis for their frequent bowel movements, especially in the morning Further observation has revealed that the pseudodiarrhea was due solely to the ingestion of coffee

The clinician is reminded that he cannot rely upon a favorable therapeutic response after the administration of nitrogen mustard (viz , prompt lysis of fever increased appetite and strength, and the passage of formed stools) as being indicative of a lymphomatous infiltration of the bowel causing a malabsorption syndrome Such a response has been forthcoming in regional enteritis and other conditions[155b]

INTESTINAL LIPODYSTROPHY

It is not difficult to appreciate why Addison's disease and systemic lupus erythematosus are usually contemplated in cases of intestinal lipodystrophy when one considers the weight loss, indefinite abdominal signs, anemia hypotension generalized skin pigmentation, fever, lymphadenopathy, polyserositis, and multiple arthritis that characterize the latter condition[160] The occurrence of diarrhea in association with normal or even decreased motility of the bowel poses an apparent paradox in patients with Whipple's disease

The presence of a hypochromic anemia, rather than one of a macrocytic nature, which does not respond to the usual treatment of sprue is consistent with the diagnosis of Whipple's disease A verrucous endocarditis has also been observed The diagnosis of Whipple's disease can be established confidently from a careful study of the peripheral lymph nodes if the characteristic accumulations of Schiff positive macrophages are found, mostly notably in the cortical areas Steroid therapy has been the only effective measure encountered to date in halting the relentless natural course of this disease[160b]

CHRONIC PANCREATITIS

In the absence of pancreatic calcification, diabetes mellitus and significant abdominal pain, the clinician might not think of chronic pancreatitis

vascular accidents The postoperative manifestations with which the patient might present are legion, and include diarrhea, steatorrhea, weakness, weight loss, abdominal pain, tetany, edema, osteoporosis, hypocalcemia, hypoproteinemia, and anemia [133b, 136]

Steatorrhea is one of the most frequently overlooked causes of unexplained nutritional illness in temperate climates, merely because it is not always considered The reader is referred to a fine symposium on the malabsorption syndrome edited by Adlersberg [153] In their review of 94 patients with idiopathic sprue, established by clinical and laboratory evidence, Bossak Wang, and Adlersberg have come to regard this condition as a complex genetically transmitted metabolic disorder that may start early in life as celiac disease, or may remain dormant for many years until it becomes manifest as either tropical or nontropical sprue [153b] They believe that many environmental factors can precipitate or trigger a "latent sprue," among which are malnutrition, tropical and nontropical infections, antibiotics, other medications, and possibly psychological disturbances

In addition to the varied gastrointestinal manifestations and the glossitis, idiopathic sprue may be initially manifested clinically by hypotension tetany, hemorrhagic episodes, bone pain, osteoporosis, clubbing, hypoproteinemia edema, and a megaloblastic anemia [152, 153] The bleeding is almost always due to the severe hypoprothrombinemia resulting from vitamin K deficiency, but interestingly is rarely encountered in tropical sprue Wang and Bossak have reported upon seven patients whose presenting hemorrhagic phenomena necessitated hospitalization, in many of whom the underlying steatorrhea was not recognized [153c] Of the aforementioned 94 patients with this malabsorption syndrome who were studied by Sencer, evidence of neurologic involvement was found in 52 per cent, including several individuals with posterolateral involvement and other evidences of a myeloradiculoneuropathy Eight of these patients had no anemia [153d] Severe mental changes were found in 11 patients, in five of whom a frank psychosis was present Although the 'sprue pattern' of the small intestine—primarily segmental distribution of the barium column in discrete masses, with hypersecretion and dilatation of the bowel lumen—is usually associated with idiopathic steatorrhea it has also been noted in secondary steatorrhea (especially Whipple's disease and lymphosarcoma) and following a subtotal gastrectomy [153e]

Finlay and Wightman, and Volwiler have stressed the fact that in addition to the malabsorption of fat in patients who do not present the classic picture of sprue detectable deficiencies of carbohydrate, nitrogenous materials water calcium, potassium, sodium iron folic acid and vitamins A B_{12} D, K and the B complex may also exist [154] The diagnosis is scientifically made if one finds more than ten per cent of the ingested fat in the stool and a low to absent serum carotene level [155] Nontropical sprue has become less difficult to treat with the availability of the adrenocortical hormones, folic acid vitamin B_{12} and the emulsifying agents [156] The remarkable improvement effected by wheat-free diets, even after the aforementioned therapies had proved ineffective, has been confirmed in the author's own experience [157] It must be emphasized that the decrease in the number of daily bowel movements and the cessation of diarrhea are *not*

necessarily indicative of diminishing fat and nitrogen losses Furthermore, it is again stressed that diarrhea need not be an essential feature of the steatorrheic syndrome

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Chronic Pancreatitis

In the absence of pancreatic calcification, diabetes mellitus and sig nificant abdominal pain the clinician might not think of chronic pancreatitis

in a patient exhibiting weight loss, an increased appetite, steatorrhea, creatorrhea, osteomalacia, and tetany[161a] The diagnosis of thyrotoxicosis, diabetic neuropathy, nontropical sprue (in which diabetes is actually quite uncommon), Whipple's disease and a calculus or small ductal cell carcinoma blocking the duct of Wirsung may receive much consideration in such instances

There have been a number of these cases which have clearly demonstrated the lack of correlation between attacks of pain and destruction of the gland In one series of 10 patients with chronic pancreatitis reported by Bartholomew and Comfort in whom pain was not a prominent feature, the progressive destruction of the gland became apparent only when calcification, steatorrhea, diabetes mellitus jaundice, or cyst formation occurred[161b] The clinician is warned against making the diagnosis of painless pancreatitis in individuals with vague chronic abdominal complaints unless steatorrhea, diabetes mellitus, or calcification do make their appearance

In the absence of previous gastric surgery, disease of the small bowel or pyloric obstruction impaired fat absorption is strongly suggestive of pancreatic disease[16?] One can only prove that an exocrine pancreatic insufficiency *is the basis of a given malabsorption syndrome by demonstrating* one or more of the following phenomena in the laboratory (1) the virtual absence of proteolytic and lipolytic enzymes in the duodenal juice, (2) the absence of a significant pancreatic response to intravenous secretin, and (3) the demonstration of an unequivocal improvement in the absorption of dietary fat and nitrogen following the administration of a potent pancreatin preparation[154b] Hyperlipemia has been observed in association with chronic pancreatitis and may even be accompanied by xanthomatosis of the eruptive type and by lipemia retinalis[163]

Since chronic relapsing pancreatitis appears to be transmitted as a mendelian autosomal dominant gene in certain families, the occurrence of these symptoms in the relative of a patient with pancreatic disease must be carefully considered[164] The early age of onset, the high incidence in females, and the absence of gallstones characterize the hereditary form of this disease

Fibrocystic Disease of the Pancreas

Fibrocystic disease of the pancreas is actually a relatively common "generalized exocrinopathy in children the systemic significance and familial aspects of which have only recently been fully appreciated[165a] The far reaching nutritional disturbances resulting from the absence of all three of the pancreatic enzymes and the steatorrhea are well known In 10 per cent of these cases however pancreatic function is partially preserved or even normal The islets of Langerhans are usually intact The focal hepatic necrosis with biliary obstruction, the abnormally high concentrations of chloride and sodium secreted by the sweat glands and the abnormal production of mucus with bronchial obstruction are equally important in determining the prognosis

The simple rapid and inexpensive finger imprint chloride method for screening and diagnosing suspected cases of cystic fibrosis of the pancreas

has already proved to be of great value (p 708),[156] especially because of the ease with which unrecognized instances of this disorder can be found among the siblings

When one considers the great percentage of children with chronic pulmonary disease (obstructive emphysema, chronic bronchopneumonia), cirrhosis of the liver and portal hypertension due to fibrocystic disease of the pancreas the importance of early diagnosis, treatment, and prophylactic measures is at once apparent if more than 10 per cent can be expected to survive their tenth year The occurrence of unexplained bronchiectasis, recurrent pneumonia or asthma in children—even after the age of one year and in the absence of significant gastrointestinal and nutritional disturbances—should prompt a search for a possible underlying cystic fibrosis of the pancreas with such simple procedures as the aforementioned finger imprint method or the sweat test Lobar atelectasis of one segment (particularly the right middle lobe) is tolerated poorly by small babies with this condition and has been successfully excised[165b] (Unfortunately, one must hasten to point out that segmental bronchiectasis is relatively infrequent in this generalized disorder)

Regional Enteritis

Despite the widespread chronic segmental granulomatous inflammation of the ileum, jejunum duodenum and stomach found at laparotomy in some patients with regional enteritis the preoperative findings may be of little diagnostic value Weight loss steatorrhea failure of growth and episodic upper abdominal distress often characterize involvement of the stomach and duodenum[166] Regional ileitis has presented itself as prolonged obscure fever masked salpingitis a mass in the cul-de-sac and symptoms suggestive of a urinary tract infection[167]

A number of concomitant visceral changes in regional enteritis are described consisting of liver infiltration and necrosis pancreatic fibrosis glomerulitis renal tubular degeneration, amyloidosis and thrombosis of the major vessels It has been shown that these lesions are actually non specific however being similar to those noted in many other chronic debilitating diseases It is also of considerable interest that the progressive sclerosing granulomatous inflammation occurring in the intestine does not involve the other viscera[169]

To state that adenocarcinoma of the jejunum is a definite complication of a stenosing jejunitis might be misleading Nevertheless, the several instances of this particular combination that are on record suggest the possibility of such a sequence especially in light of the relative rarity of jejunal carcinoma[170]

Clinicians should be aware of the shortcomings of barium enema studies when a regional enteritis is suspected, and of the need for examination of the small bowel by x ray when the barium enema studies are regarded as negative In one series of 38 patients who were treated conservatively at the Mayo Clinic suggestive features of this disease could be found in only 14 while in 13 instances a normal appearance of both the colon and the terminal part of the ileum was encountered[168b] (It is

of further interest that progression of the disease to the colon could be shown in only two patients)

A number of vexing considerations pertaining to the role of surgery in the management of regional enteritis will be discussed under Group XV (p 488) While pregnancy poses more of a threat to women who have ulcerative colitis the pregnant state also tends to exert an unfavorable influence on patients with regional enteritis [168c]

Ulcerative Colitis

In cases where the function of the ascending colon is preserved in ulcerative colitis, there may be few symptoms referable to the bowel In fact, a number of these patients often present a wide variety of extra colonic manifestations, of which the erythema nodosum-arthralgia conjunctivitis triad is the most impressive [171a] In managing the seriously ill patient with ulcerative colitis, one must repeatedly entertain such possible complicating factors as amyloidosis hepatitis pyelonephritis, thrombophlebitis uveitis, hypoproteinemia, nutritional deficiencies, hypokalemia, and pseudopolyposis—each of which poses its own added therapeutic problem [1 1b]

In view of the uncertain causation of nonspecific ulcerative colitis and the ability of the 'hyperactive' colon to react to a number of infectious and noninfectious agents in a similar manner, the clinician would do well to consider certain 'specific causes in the atypical case In addition to tuberculosis amebiasis and bacillary dysentery other less apparent causes include lymphopathia venereum, scleroderma, acute vasculitis of the large bowel, and secondary amyloidosis associated with lymphoma [172]

CHRONIC RENAL DISEASE

The diagnoses of *uremia and chronic renal disease* have repeatedly proved elusive because of the insidious nature and the diverse presenting symptoms of these conditions In the absence of hypertension oliguria and edema, the easy fatigability headaches, anorexia, vague gastrointestinal complaints, visual disturbances, hiccup anemia hemorrhagic phenomena, and pruritus may give no clue to this state until the urine and blood are studied [173] If the patient drinks adequate fluids and has a large urine output even the usual blood chemistries might approach normal [174] It is not uncommon for clinicians to insist upon diagnosing as a collagen disease what subsequently proves at the autopsy table to have been a case of ordinary chronic glomerulonephritis [175a] The significance of pyelonephritis (p 109) and polycystic disease of the kidneys (p 422) is discussed under Groups IV and XIV respectively The subject of acute and subacute tubular necrosis will also be considered later (p 458)

The occurrence of a diffuse glomerulitis with red cell casts in a patient who does not have typical acute or subacute glomerulonephritis raises several possibilities These include disseminated lupus erythematosus poly arteritis, the embolic glomerulonephritis associated with subacute bacterial

endocarditis sterile embolization to the kidneys, scleroderma renal disease and Wegener's granulomatosis—but only infrequently acute renal ischemia or malignant nephrosclerosis If a patient with a known malignancy suddenly exhibits an unexplained, progressive and fatal uremia, the possibility of an acute generalized vasculitis with an extensive necrotic glomerulitis might also be entertained [156c]

In the young male patient with a chronic nephritis and progressive renal failure, the clinician would do well to seek out both the familial history and associated nerve deafness that characterize the syndrome of hereditary nephropathy and deafness (p 423)

It should be recognized that there may be widespread pulmonary changes by x ray in glomerulonephritis due to the transudation of blood into the alveoli (presumably due to alterations in the capillary permeability) Furthermore such pulmonary changes can be found with only a mild nephropathy and in the absence of cardiac enlargement or failure [175b] One must hasten to point out however, that these pulmonary changes cannot be specifically characterized as a uremic or nephritic pneumonitis, since they have been found in a number of other conditions, including rheumatic pneumonitis[457] and following the chemical ganglionic blockade that occurs with the use of certain antihypertensive drugs [460]

It is important to be cognizant of the fact that both acute and chronic renal insufficiency may account *per se* for marked elevations in the plasma amylase This occasionally bears considerable clinical emphasis, since acute uremic abdominal crises can occur under these circumstances which may closely simulate bouts of acute pancreatitis [176] Pericarditis occurs in about 18 per cent of patients with acute renal failure but does not carry the associated poor prognosis as in the case of chronic renal failure [177a] Contrary to the general belief there may be large amounts of pericardial fluid associated with uremic pericarditis and a fatal cardiac tamponade can actually result [177b]

Bleeding occurs frequently in uremia from all causes It is a particular problem in some instances of acute renal insufficiency Whereas such hemorrhage was previously attributed to vascular defects, more recent studies tend to incriminate defects in the platelets, both of a quantitative nature (i e , less than 150 000 per cu mm) and of a qualitative type (i e , abnormal prothrombin consumption in patients with adequate numbers of platelets) [177d]

It must be emphasized constantly that the renal damage may be of varying and unpredictable degree and character especially in relation to the induction of electrolyte imbalances The diseased kidney can lose or retain water, sodium chloride phosphate calcium, potassium or amino acids Consequently, various clinical syndromes have been produced by isolated dysfunctions of the renal tubules relating to *defects in tubular absorption and resorption* These include nephrogenic diabetes insipidus, renal glucosuria, "salt losing nephritis," renal hypokalemia chloride acidosis pseudohypoparathyroidism, vitamin D resistant rickets and the Fanconi syndrome (*vide infra*) [178] However, one should bear in mind when discussing the various clinical types of tubular dysfunction that disturbances

of further interest that progression of the disease to the colon could be shown in only two patients)

A number of vexing considerations pertaining to the role of surgery in the management of regional enteritis will be discussed under Group XV (p 488) While pregnancy poses more of a threat to women who have ulcerative colitis, the pregnant state also tends to exert an unfavorable influence on patients with regional enteritis[168c]

Ulcerative Colitis

In cases where the function of the ascending colon is preserved in ulcerative colitis, there may be few symptoms referable to the bowel In fact a number of these patients often present a wide variety of extra colonic manifestations, of which the erythema nodosum arthralgia conjunctivitis triad is the most impressive[171] In managing the seriously ill patient with ulcerative colitis, one must repeatedly entertain such possible complicating factors as amyloidosis hepatitis, pyelonephritis, thrombophlebitis uveitis hypoproteinemia nutritional deficiencies, hypokalemia, and pseudopolyposis—each of which poses its own added therapeutic problem[171b]

In view of the uncertain causation of nonspecific ulcerative colitis and the ability of the 'hyperactive' colon to react to a number of infectious and noninfectious agents in a similar manner, the clinician would do well to consider certain "specific" causes in the atypical case In addition to tuberculosis amebiasis and bacillary dysentery other less apparent causes include lymphopathia venereum scleroderma, acute vasculitis of the large bowel and secondary amyloidosis associated with lymphoma[17]

CHRONIC RENAL DISEASE

The diagnoses of *uremia and chronic renal disease* have repeatedly proved elusive because of the insidious nature and the diverse presenting symptoms of these conditions In the absence of hypertension oliguria and edema, the easy fatigability headaches, anorexia, vague gastrointestinal complaints visual disturbances, hiccup, anemia, hemorrhagic phenomena, and *pruritus may give no clue to this state until the urine and blood* are studied[173] If the patient drinks adequate fluids and has a large urine output, even the usual blood chemistries might approach normal[174] It is not uncommon for clinicians to insist upon diagnosing as a collagen disease what subsequently proves at the autopsy table to have been a case of ordinary chronic glomerulonephritis[175a] The significance of pyelonephritis (p 109) and polycystic disease of the kidneys (p 422) is discussed under Groups IV and XIV respectively The subject of acute and subacute tubular necrosis will also be considered later (p 458)

The occurrence of a diffuse glomerulitis with red cell casts in a patient who does not have typical acute or subacute glomerulonephritis raises several possibilities These include disseminated lupus erythematosus, polyarteritis, the embolic glomerulonephritis associated with subacute bacterial

normal salt intake (5 to 8 gm per diem), and can be relieved by the dai intake of 10 to 20 gm of salt

2 The clinical state cannot be relieved by desoxycorticosterone ac tate or, alternatively, steroids are present in the urine in relatively norm quantities

3 Evidence of renal disease is present (low specific gravity, polyuri anemia elevated plasma urea and creatinine) and persists on a high salt intake

Although advanced salt losing nephritis probably represents an un usual variant of chronic glomerulonephritis or pyelonephritis, the recog nition of this condition as a separate entity is merited because of th ease of specific therapy once it is recognized and its undoubted great frequency in milder forms The pathogenesis of this state is most likel due to the more rapid deterioration of tubular function (necessary for th resorption of sodium chloride) than the concomitant deterioration glomerular function

When confronted with a puzzling case of uremia in the presence of normal blood pressure one must always consider the *potentially reversib types of renal insufficiency* Particular attention should be directed to th possibilities of primary hyperparathyroidism vitamin D poisoning, th milk alkali syndrome acute or subacute bacterial endocarditis, fluid an electrolyte depletions salt wasting nephritis postrenal obstruction, and acute urinary tract infection superimposed upon chronic nephritis or co genital polycystic disease of the kidneys[150]

Since an acidosis is usually found in uremia even after considerab vomiting has occurred the mere presence of a mild alkalosis and a norm serum carbon dioxide value should make one suspicious of the milk alka syndrome[151] The finding of azotemia accompanied by an unusual norm chromic and normocytic anemia that is refractory to the usual hematin agents necessitates a detailed investigation for possible vitamin D se medication[152] The diffuse vacuolar nephropathy and secondarily impaire renal function that is encountered in many conditions in which marke hypokalemia exists will be discussed later in this chapter (p 80) This particularly prone to occur if there has been pre-existing renal abnormality

Unlike other types of chronic nephritis hypertension is usually no associated with the renal failure due to nephrocalcinosis from variou causes The massive release of nucleoproteins associated with the dru therapy of leukemia and polycythemia vera may be reflected in the el vated blood uric acid levels (with or without clinical gout) acute ren failure, and the formation of uric acid calculi (p 184)[153] Patients wit chronic renal failure due to gout myeloma polyarteritis and disseminate lupus erythematosus have occasionally exhibited striking improvement fo lowing specific therapy Muehrcke and his colleagues have exhaustivel reviewed the clinical and pathologic features of lupus nephritis[931] Whi cortisone and its analogs must be used with great caution in sarcoidos (preferably with the patient being placed on isoniazid) the successfu response of the hypercalcemia to steroid therapy and the gratifying im

in *both* the proximal and distal tubules can usually be demonstrated, even though the features of one predominate

When it is not iatrogenically induced by prolonged therapy with either acidifying salts or Diamox *hyperchloremic tubular acidosis* may be a manifestation of distal renal tubular dysfunction (Butler Albright's syndrome)[188] Since the aspect of renal function involved is concerned not only with completing the resorption of water and electrolytes, but with the production of ammonia and the elaboration of an acid urine, a striking polyuria occurs in this disorder that is characterized by an alkaline urine of low specific gravity very low in ammonia but rich in such essential cations as sodium, potassium and calcium The prolonged losses of bicarbonate in the urine stimulate excessive chloride resorption and the ensuing compensatory hyperchloremic acidosis The changes in the skeleton may be those of osteitis fibrosa, or of rickets and osteomalacia Nephrolithiasis and nephrocalcinosis can result from the concomitant presence of an alkaline urine and hypercalciuria Various alkalinizing regimens have been used with success in this condition the most popular one being Shohl's preparation containing a mixture of citric acid and sodium citrate One must be careful not to induce a severe hypokalemia however, in view of the associated loss of potassium and the forcing of sodium salts

Another interesting variant of the renal tubular dysfunction syndromes is "*phosphate diabetes*" in which the inherited congenital defect in the proximal tubules results in the excessive loss of phosphate Even though this condition bears no relationship to diabetes mellitus, renal glucosuria may also be present (but without hyperglycemia) There are approximately 40 cases on record of rickets and osteomalacia due to this disorder the majority of which proved to be "vitamin D resistant" (as is the case in the Lignac Fanconi syndrome)[189] The profound loss of phosphate in the urine due to its impaired resorption leads in turn to marked hypophosphatemia, excessive excretion of calcium from the intestine, and hypocalcemia

Secondary parathyroid hyperplasia may add confusing chemical or bone and joint features to the picture of chronic renal disease The *renal osteodystrophy* can consist of osteomalacia osteoporosis, osteosclerosis, subperiosteal bone resorption in the phalanges (a very characteristic feature), cystic changes, widened irregular epiphyseal lines, or various combinations of these findings Bone pain in the spine pelvis and legs is commonly the presenting symptom Since striking degrees of hypocalcemia hyperphosphatemia and rises in the alkaline phosphatase are usually associated with advanced changes and inasmuch as most of the reports have described cases occurring in children this syndrome might readily be missed in adults unless it is continually considered in the differential diagnosis of obscure skeletal disorders[178b] Tetany is usually a late manifestation of renal failure and the attendant hypocalcemia (since the acidosis increases the proportion of ionized calcium)

Levere and Wesson[179] have set forth the following minimal criteria for the diagnosis of a *salt losing nephritis* in order to distinguish it from the other salt losing states

1 The signs and symptoms related to dehydration are present on a

degree of azotemia The importance of considering the possibility of magnesium intoxication in instances of acute renal failure where the clinical and electrocardiographic findings suggest potassium intoxication—but in which there is little or no hyperkalemia—is pointed out

Experience and prolonged observation have repeatedly shown the wisdom of regarding most cases of "*lipoid nephrosis*" as the nephrotic phase of a chronic glomerulonephritis I have cared for several virtually asymptomatic patients with long standing anemia and relatively normal blood urea nitrogen and creatinine levels who have had well documented histories of glomerulonephritis or pyelonephritis with massive proteinuria extending over prolonged periods (ranging up to twenty five years) Schreiner has re-emphasized the necessity for rigid criteria in making the diagnosis of chronic (or "pure") nephrosis[185] These should include the absence of any known causes for the nephrotic syndrome the histologic demonstration of membranous glomerulonephritis along with the absence of proliferative or degenerative changes in the glomeruli, and a reasonable passage of time for the evolution of the lesions of glomerulonephritis if they are to occur Rare instances of genuine acute glomerulonephritis have been reported in which there is a nephrotic component in the acute hemorrhagic phase[185] The predisposition to streptococcal and pneumococcal infections in nephrosis and the 'nephrotic crises' are discussed under Group IV (p 142)

Nephrosis may be a familial disorder One recent study has shown the variability of the clinical and pathologic manifestations of nephrosis as it affected four children in one family from which it would appear that a single basic pathogenetic mechanism was operative[186a]

Other causes of the *nephrotic syndrome* include the collagen diseases, amyloidosis, intercapillary glomerulosclerosis secondary syphilis, leptospiral infections, renal vein thrombosis and various poisonings or idiosyncrasies (tridione therapy paramethadione hypertonic glucose or sucrose solutions, poison oak dermatitis) that injure the glomerular capillary membrane[185, 186] Since it is unusual for either nephrosclerosis or chronic glomerulonephritis to reach an advanced state of renal insufficiency without significant hypertension, serious consideration to the possibility of an amyloid nephrosis must be given when this type of a situation presents itself in association with massive albuminuria and hepatomegaly

Several added comments are in order concerning clues to the diagnosis of *bilateral renal vein thrombosis* as a cause of the nephrotic syndrome in view of the possible salutory therapeutic effect of anticoagulants, surgery, or both These include the following

1 The development of the nephrotic syndrome in an adult with no past history or evidence of renal disease

2 The association of nephrosis with other evidences of intravascular thrombotic-embolic phenomena, or with various diseases which predispose to thrombosis by stasis and inflammation Maternal diabetes mellitus may predispose to the development of renal vein thrombosis in infants, even in the absence of dehydration or sepsis[187d]

The subject of the "hepatorenal syndrome" is discussed in the next chapter (p 97) A number of considerations pertaining to the diagnosis and management of postoperative and post-traumatic renal failure are considered under Group XV (pp 458–461)

From his extensive experience with the problem of renal failure, Merrill has cited the following additional circumstances under which the failure of urinary secretion might be reversible [1800]

1 While the simultaneous occlusion of both ureters by renal calculi is quite unusual, it is important to bear in mind the possibility of oliguria due to the obstruction of one ureter by a renal stone when the other kidney is not functioning Small calculi may be overlooked if they are radiolucent (as in the case of uric acid calculi) or when they are lodged at the terminal end of the ureter

2 Blood clots that form after episodes of massive hematuria may occlude one or both ureters Carcinoma of the cervix and carcinoma of the prostate gland constitute two situations in which the renal suppression from the carcinomatous spread may be either acute or chronic and is potentially reversible

3 Patients with mild prostatism are potential candidates for acute urinary retention when they are placed on a number of medications Among the most important offenders are the ganglionic blocking agents and the antihistaminics

4 Acute renal failure is probably due to parenchymal renal involvement rather than obstruction when the probing ureters meet no obstruction, when the plain films of the abdomen reveal kidney shadows of normal size, and when no urine can be obtained from the renal pelvis

5 One must be very careful about the forcing of fluids in the oliguric patient—even when there is apparent dehydration—if acute renal damage is suspected This consideration is particularly germane when the kidneys are unable to concentrate the urine satisfactorily Replacement fluid therapy should be attempted under these circumstances *only* when the urine concentrates to 1 020 or better One must remember that the patient with acute renal failure cannot concentrate urine even when profound oliguria is present

6 By the time most patients present themselves with renal failure that resulted from nephrotoxins, the nephrotoxic heavy metals or intravascular hemolysis little improvement can be expected It is of interest that renal damage appears to occur more often as the predominant injury when carbon tetrachloride is inhaled rather than when it is ingested

7 Merrill and others have observed patients with bilateral cortical necrosis of the kidneys who recovered This complication is not necessarily limited to the various complications of pregnancy (most notably premature separation of the placenta) (p 460)

8 Whereas acute tubular necrosis is characterized by oliguria rather than anuria, anuria tends to occur in the patient with thrombosis of the renal vessels or with an extensive glomerulonephritis (*vide infra*)

9 The management and prevention of hypoxia, overhydration heart failure, and potassium intoxication may be of greater importance to the survival of the patient with acute renal failure than overconcern about the

polyuria can persist for over three months) and that the 24 hour sodium loss in the urine could range from 250 to 1000 mEq In further studies carried out on this particular problem, Merrill and his colleagues concluded that the basic derangement in renal function consisted of suppressed tubular resorption—predominantly in the proximal segments—and that the diuresis was the result of the delivery into the urine of the excessive amounts of sodium and chloride being filtered through the glomeruli, most of which ordinarily should have been reabsorbed [19b] This acquired type of "water losing nephritis" (which is not responsive to vasopressin) may be reversible if treated before the onset of azotemia albuminuria, and renal tract infection [193] One must never lose sight of the significant frequency with which middle-aged and elderly men—either with manifest or unrecognized prostatic disorders—can be thrown into acute urinary retention by vigorous diuretic therapy [194]

The Lignac Fanconi Syndrome and Renal Aminoaciduria

The *Lignac Fanconi disease* (cystinosis, the de Toni-Fanconi syndrome) is one of the very interesting tubular acidosis syndromes to which reference was made earlier in this section It is quite uncommon and occurs primarily in infants and children This disorder is characterized by retarded development, dwarfism muscle weakness rickets renal changes the storage of cystine crystals in the cells of the reticuloendothelial system, and aminoaciduria [195]

Eighteen instances of the Fanconi syndrome occurring in adults have been reviewed by Wallis and Engle [195a] These investigators employed the following diagnostic criteria osteomalacia with hypophosphatemia and pseudofractures, renal glucosuria, aminoaciduria and no hyperaminoacidemia It is not unlikely that a number of instances heretofore diagnosed as either Milkman s syndrome or "vitamin D resistant rickets" are related to the adult Fanconi syndrome

This disorder is due to a congenital and probably familial metabolic defect in which the proximal renal tubules fail to resorb properly glucose amino acids, inorganic phosphate and possibly bicarbonate The inheritance pattern is that of a recessive gene, although there are no demonstrable abnormalities in the parents [178c] There ensues a hyperchloremic acidosis, stemming in large measure from the depletion of bicarbonate It usually presents itself in the form of osteomalacia or rickets because of the great loss of calcium as base, even though both the blood calcium and urea nitrogen may be normal [196] A reduced phosphorus resorption index (i e, lower than 0 86) might prove to be a useful screening test in diagnosing primary or secondary hyperphosphaturia (p 819) Inasmuch as marked hypouricemia is encountered only in Wilson s disease and the de Toni Fanconi syndrome the very simple determination of the blood uric acid may be helpful when the latter disorder is being considered [363]

The cystine deposits in the cornea and conjunctiva the typical crystals found on bone marrow aspiration and paper partition chromatography of the urine can all be diagnostic of this unique metabolic derangement [197a] Several instances of benign cystinosis have been first identified by alert

3 A progressively downhill course without the remissions common to the other types of nephrosis

4 The disappearance of nonspecific myocarditis and congestive heart failure with the onset of the nephrotic syndrome

5 The presence of recurrent diffuse abdominal and loin pain

6 The failure of the intravenous dye to be excreted by the kidneys on intravenous pyelography in the presence of normal retrograde pyelograms

7 The histologic absence of other possible causes in material obtained by percutaneous renal biopsy [187]

Hydronephrosis can be so insidious in onset and produce such minor or so few urinary symptoms that its discovery by pyelography or laparotomy often comes as a complete surprise Most experienced urologists know of instances where the prime manifestations of this disorder were referable to the gastrointestinal tract or gallbladder resulting in several major abdominal explorations being performed before the underlying urinary tract disease was suspected

In this regard, it is not amiss to call attention to the fact that it is very possible for a man to have few urologic symptoms from *"silent prostatism"* despite a large decompensated urinary bladder with considerable residual urine and severe renal damage due to the associated back pressure Dick has collected a group of 16 fairly intelligent patients over a six year period who had been seen regularly by their physicians, yet each of whom *already had serious urinary tract damage before the prostatic obstruction* was recognized [190] It is of interest to recount the following immediate reasons for their seeking medical advice (1) the development of gastrointestinal symptoms (nausea vomiting, flatulence, constipation), (2) the development of symptoms resulting from uremia and severe anemia (weakness, easy fatigability, dyspnea) (3) the discovery of a mass in the lower abdomen and (4) the desire for a thorough medical examination These same considerations apply when *impaired innervation of the urinary bladder* is present in a variety of nervous system disorders (diabetic neuropathy multiple sclerosis, tabes dorsalis, spinal cord injury and poliomyelitis), resulting in the sequence of vesicoureteral reflux hydroureter, and finally hydronephrosis

There are a number of *fluid and electrolyte aberrations in chronic lower urinary tract obstruction*, most notably when caused by an enlarged prostate Lapides has demonstrated the universal lowering of the plasma bicarbonate and elevation of the nonprotein nitrogen but an *inconstancy* and variability of the serum sodium, chloride and potassium levels [191] Wilson, Reisman, and Moyer have also emphasized the marked degrees of salt and water depletion that are prone to follow decompression of the bladder in these patients [192] Certain cases of profound polydipsia polyuria, and hyposthenuria (a urine with an osmolar concentration lower than that of plasma or with specific gravities consistently below 1 010) have been *found* to be due to obstructive uropathies Some idea of the magnitude of the changes following relief of the obstruction can be obtained by noting that the 24-hour urine volumes have ranged from 4 5 to 15 liters (which

become manifest, some human beings have shown lesions within several weeks after the onset of the suppurative process [199a]

Secondary amyloidosis is the leading cause of death in leprosy and is directly related to the renal involvement This complication may occur in relatively young people who have had active lepromatous leprosy for only a few years [200] It is important to appreciate the fact that apparent regression of the amyloidosis secondary to tuberculosis as judged by a reversal of the Congo red retention test, has been reported in several cases following intensive antimicrobial therapy [201]

Secondary amyloidosis is also encountered in syphilis, endocarditis, and carcinoma An unusual incidence of secondary amyloidosis in hypernephroma both in the resected kidney and distributed throughout the body, has been encountered [203] Consequently, one should not automatically attribute proteinuria and azotemia to the renal neoplasm, especially if hepatosplenomegaly is also present

A reverse situation pertaining to increasing incidence holds true for primary amyloidosis and the *amyloidosis associated with myeloma, leukemia* or *lymphoma* In these instances the heart, skin tongue, gastrointestinal tract, and skeletal muscle are most notably involved This diagnosis should be entertained in cases of unexplained cardiomegaly heart failure, apparent constrictive pericarditis liver failure sprue gastrointestinal hemorrhage, and adrenocortical insufficiency in patients over fifty years of age [5, 207] The same consideration applies in the presence of chronic purpura when thick, gelatinous material is aspirated from the bone marrow and a plasmacytosis is found [204] Primary amyloidosis should also be considered when a chronic sensory neuropathy or hoarseness is associated with significant electrocardiographic changes or the aforementioned cardiac abnormalities [205]

Even though the initial search for myeloma in the patient with primary amyloidosis is negative, evidence for its presence may subsequently be found if the patient lives long enough Amyloidosis has been observed by a number of clinicians in patients with Hodgkin's disease who have received several courses of nitrogen mustard and who have survived for an unusually long time [198] While localized amyloid tumors (particularly in the respiratory tract) are usually benign, there are known instances of systemic amyloidosis occurring after the excision of such local accretions [198]

The tongue changes in primary systemic amyloidosis are depicted in Figure 35 (Atlas page 22) The cutaneous manifestations of localized amyloidosis are pictured in Figure 98 (Atlas page 63)

Although uremia is not very common in the primary form of the disease, it is frequently a striking feature with the 'myeloma kidney' Renal failure is usually the terminal event in patients with secondary amyloidosis in contrast to occurrence of heart failure in the primary cases The clinician must be cognizant of the fact that a false-positive Congo red test might occur in the presence of any massive proteinuria Another fascinating manifestation of this disease—with or without a coexisting myeloma—is the appearance of a bilateral median nerve neuritis This so-called carpal tunnel syndrome is due to involvement of both the nerve and tendon sheaths [98] Dahlin has cautioned against relying too strongly

ophthalmologists, following the demonstration of cystine crystals in the cornea and conjunctiva in patients coming for routine refraction examinations[197b] This condition differs from benign cystinuria in which there are no depositions of crystals in the tissues, even though the cystine level in the urine is elevated (p 422)

The biochemical sign of *renal aminoaciduria* is coming into greater diagnostic prominence and merits a brief discussion (p 699) Harrison and Harrison have pointed out the fact that aminoaciduria might variously result from either those disturbances of the metabolism of amino acids which cause their concentration in the plasma to increase (as in the case of severe liver disease), or from defects in the renal tubular resorption mechanism of the amino acids in individuals who have normal (or even decreased) blood levels of these substances[195c] In either instance, the defect may be limited to a specific amino acid or a small group of amino acids, or the defect may be total, involving practically all the amino acids Under ordinary dietary conditions, it would be rare for the urinary loss of amino acids *per se* to be of sufficient magnitude to induce amino acid deficiencies The formation of cystine calculi in cystinuria is the one significant disorder that can at present be attributed to an excessive aminoaciduria (p 422) The importance of an early biochemical diagnosis of phenylketonuria as it relates to prophylaxis and therapy is discussed elsewhere (p 369)

The mechanism of renal tubular resorption of amino acids is highly susceptible to a wide variety of inborn errors of cell metabolism, vitamin deficiency states, and toxic agents As a consequence, a high aminoaciduria may well become a valuable test for the early diagnosis of intoxication from a number of heavy metals encountered in industry, most notably lead, uranium, and cadmium (In normal individuals, the urinary excretion of free amino acids is very slight, accounting for only 1 to 2 per cent of the total urine nitrogen) It is also becoming evident that the Fanconi syndrome (renal aminoaciduria, renal glucosuria, phosphaturia, and hypophosphatemic rickets or osteomalacia) may not only represent a congenital metabolic defect but also an acquired renal tubular injury Since vitamin D appears to influence the renal tubular mechanisms dealing with the resorption of amino acids and phosphate either directly or indirectly, its administration may be of value in reducing the amounts of amino acids excreted

SYSTEMIC AMYLOIDOSIS

Secondary amyloidosis involving the liver, spleen, kidneys, and adrenals is being encountered less commonly now with the better control of tuberculosis, chronic pyogenic infections (actinomycosis, osteomyelitis, bronchiectasis, renal infections, chronic fistulas), and rheumatoid arthritis[198] The diagnosis of amyloidosis should also be considered in the patient with chronic ulcerative colitis exhibiting albuminuria, a very firm and enlarged liver or spleen, and considerable suppuration in the wall of the colon[199] Although months or years are usually required for the disease to

become manifest, some human beings have shown lesions within several weeks after the onset of the suppurative process [199c]

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on the sign of macroglossia.[202] He also warns against the intravenous injection of Congo red in the presence of extensive skin deposits.

It must be pointed out that there is considerable overlapping in the distribution of the deposits in both "primary" and "secondary" amyloidosis, and that an accurate differentiation between these two groups on the basis of staining reactions alone is somewhat dubious.[206] Attention is directed to the unpredictable staining of primary amyloid, in contrast to the constant affinity of the tissues involved by secondary amyloidosis for certain dyes (Congo red, crystal violet, methyl violet). However, a biopsy of either the gingiva or liver may be the only clinical way of establishing the diagnosis of primary amyloidosis ante mortem (the former being preferred in view of the likelihood of severe hemorrhage from needle puncture in this disease) (p. 794). The pathologist should nevertheless attempt to differentiate amyloid from the paramyloid deposits found in sarcoidosis and systemic lupus erythematosus. These disorders and other disturbances of the immune mechanism in the reticuloendothelial system may ultimately prove to be etiologically related to amyloidosis.[0]

Here again, an occasional family pedigree is encountered in which the familial aspects of a disease that is not usually regarded as being hereditary are demonstrated in a striking manner.[09] These instances of familial primary systemic amyloidosis may be uncovered by the demonstration of an atypical alpha-2 globulin in their serum electrophoretic patterns.

HEMOCHROMATOSIS

Another important systemic disease which continues to be overlooked by clinicians is hemochromatosis.[210] With the ready availability of serum iron studies and the aid of the liver biopsy technique, I have encountered several of these patients who would have otherwise been considered as instances of either alcoholic-type cirrhosis of the liver or diabetes mellitus with liver enlargement due to fatty infiltration. Neither the diffuse bronzing nor the slate-gray metallic tint of the skin was present in these cases.

Primary iron storage disease may also exhibit familial ramifications. This is a highly significant consideration in dealing with the relatives of these patients, should suggestive early evidence of this disease be found in them. Considerable preservation of body function can be achieved in this situation by prophylactic advice and therapy (diet, repeated venesections, chelating agents). Furthermore, hepatoma occurs four to five times more frequently in hemochromatosis than in Laennec's cirrhosis.[210a]

Bizarre abdominal pain and symptomatology may be very prominent in hemochromatosis.[211] More recently, emphasis has been placed upon the cardiac involvement produced by the pigment deposition, resulting in heart block and congestive failure.[212] It should also be appreciated that this disease can involve practically the entire endocrine system, in which case diabetes mellitus might not be encountered. When present, the pigmentation occurs in the axillae, groins, mucous membranes, about the genitalia, and is particularly accentuated in those areas exposed to the sun. Loss of hair, xeroderma, pruritus and purpura may coexist. If a skin biopsy is sought, it should not be obtained from the legs, skin folds, or over pressure

or other irritated areas. The anemia can be enhanced by the added factor of *hypersplenism complicating the cirrhosis and portal hypertension*.

The cutaneous manifestations of hemochromatosis are depicted in Figure 52 (Atlas page 32).

In suspected cases of hemochromatosis, one might look for an increased density of the liver, and a double contour line along the diaphragmatic border resulting from the extensive iron deposition. Although very unusual, misleadingly low serum iron levels (as low as 60 micrograms per cent) have been associated with hemochromatosis.[210a] A therapeutic diagnostic test for the presence of excessive iron stores employing Versenate is cited in Section XII of Part II (p. 817).

The possibility of a *secondary hemochromatosis* should be entertained in chronically anemic patients who have been given either prolonged iron therapy or multiple transfusions, especially in the presence of a severe hemolytic process such as Cooley's anemia.[214, 11] In this regard, it is of interest that the body normally contains a total of approximately 4 grams of iron. When the level of 20 grams is approached (comparable to the amount found in 80 transfusions of citrated blood), the signs and symptoms of hemochromatosis often appear. The introduction of the ferrous sulfate chelate hematinics on the therapeutic scene—substances which can effectively enhance the intestinal absorption, transport, and assimilation of this metal in the body—promises to contribute to the increased incidence of hemochromatosis. The same applies to the injudicious use of the parenteral iron preparations now available.

It is not amiss to point out here that a number of cases of *acute ferrous sulfate poisoning*—many of which were fatal—have been reported in young children following the accidental ingestion of this drug. In these patients a characteristic hemorrhagic necrosis of the peripheral or periportal portions of the liver lobules is noted.[215]

PORPHYRIA

The author has often felt that had he previously utilized a classified list when considering his problem cases, the diagnosis of either the intermittent acute or *chronic forms of porphyria (or porphyrinuria) of the* "hepatic" type might have been correctly considered more frequently. The term "porphyria" denotes disease states characterized by the excretion of relatively large amounts of urinary uroporphyrins, either preformed or as their precursor, porphobilinogen.[17, 218] While the substance itself is *colorless in freshly voided alkaline urine, it is fortunately possible to* detect porphobilinogen rather easily by the Watson-Schwartz modification of the Ehrlich reaction for urobilinogen.

The abdominal triad of colicky pain, vomiting, and constipation with an associated leukocytosis has led to a number of unnecessary abdominal explorations in this disease. One needs only to enumerate the other manifestations of nervousness (or even delirium and psychosis), red urine, polyneuritis, light sensitivity, hepatic dysfunction, and hypertension to be reminded that here is another "great mimic."[219] In addition to the blisters and erosive lesions, a diffuse or mottled melanin pigmentation that is

on the sign of macroglossia[202] He also warns against the intravenous injection of Congo red in the presence of extensive skin deposits

It must be pointed out that there is considerable overlapping in the distribution of the deposits in both "primary" and "secondary" amyloidosis, and that an accurate differentiation between these two groups on the basis of staining reactions alone is somewhat dubious[206] Attention is directed to the unpredictable staining of primary amyloid, in contrast to the constant affinity of the tissues involved by secondary amyloidosis for certain dyes (Congo red crystal violet, methyl violet) However, a biopsy of either the gingiva or liver may be the only clinical way of establishing the diagnosis of primary amyloidosis ante mortem (the former being preferred in view of the likelihood of severe hemorrhage from needle puncture in this disease) (p 791) The pathologist should nevertheless attempt to differentiate amyloid from the paramyloid deposits found in sarcoidosis and systemic lupus erythematosus These disorders and other disturbances of the immune mechanism in the reticuloendothelial system may ultimately prove to be etiologically related to amyloidosis[207]

Here again, an occasional family pedigree is encountered in which the familial aspects of a disease that is not usually regarded as being hereditary are demonstrated in a striking manner[209] These instances of familial primary systemic amyloidosis may be uncovered by the demonstration of an atypical alpha 2 globulin in their serum electrophoretic patterns

HEMOCHROMATOSIS

Another important systemic disease which continues to be overlooked by clinicians is hemochromatosis[210] With the ready availability of serum iron studies and the aid of the liver biopsy technique, I have encountered several of these patients who would have otherwise been considered as instances of either alcoholic type cirrhosis of the liver or diabetes mellitus with liver enlargement due to fatty infiltration Neither the diffuse bronzing nor the slate-gray metallic tint of the skin was present in these cases

Primary iron storage disease may also exhibit familial ramifications This is a highly significant consideration in dealing with the relatives of these patients, should suggestive early evidence of this disease be found in them Considerable preservation of body function can be achieved in this situation by prophylactic advice and therapy (diet repeated venesections, chelating agents) Furthermore hepatoma occurs four to five times more frequently in hemochromatosis than in Laennec's cirrhosis[210a]

Bizarre abdominal pain and symptomatology may be very prominent in hemochromatosis[211] More recently emphasis has been placed upon the cardiac involvement produced by the pigment deposition, resulting in heart block and congestive failure[212] It should also be appreciated that this disease can involve practically the entire endocrine system, in which case diabetes mellitus might not be encountered When present, the pigmentation occurs in the axillae groins, mucous membranes, about the genitalia, and is particularly accentuated in those areas exposed to the sun Loss of hair, xeroderma pruritus and purpura may coexist If a skin biopsy is sought, it should not be obtained from the legs, skin folds, or over pressure

erythema multiforme, vascular purpura, fixed eruptions, eczematoid lesions, and bullous eruptions), (3) systemic vascular allergies, (4) the collagen disorders (particularly lupus erythematosus and polyarteritis), (5) bronchial asthma, (6) cholangiolitic hepatitis, and (7) coronary insufficiency (observed in several instances of penicillin reactions)

It is emphasized that these responses can occur from small doses of the noxious medication, and that they need bear no relationship to drug intoxication Furthermore the therapist must be aware of the fact that an allergic reaction may be triggered by the concurrent administration of two agents—either of which could produce a hypersensitivity response—when one alone did not do so This is particularly well demonstrated in the case of the infectious mononucleosis-like syndrome stemming from combined antituberculous therapy with PAS and INH[774] Cross sensitization of sensitized individuals to related chemical compounds will pose an ever increasing problem as the number of synthetic drugs in the physician's pharmacopeia is extended Such reactions are well known among the sulfonamides the procaine anesthetics, and the barbiturates

There is increasing evidence that either the hypersusceptibility or hyposusceptibility of certain individuals to drugs (and al o to disease—for example, the decreased mortality from malaria in individuals with sicklemia) may be manifestations of otherwise latent and innocuous genetic traits or enzyme deficiencies Motulsky has reviewed a number of these possible genetically conditioned drug reactions[277] The following instances are briefly cited in this regard

1 The development of a hemolytic anemia from average doses of sulfanilimide or primaquine and its chemically related drugs by American Negroes, but only by a small number of Caucasians (apparently related to glucose-6-phosphate dehydrogenase activity)

2 The development of a hemolytic anemia from naphthalene and nitrofurantoin (Furadantin) (probably associated with the sulfhydryl defect responsible for the above mentioned sensitivity to primaquine)

3 Prolonged apnea following the use of the muscle relaxant succinylcholine chloride (Anectine) (apparently related to the familial deficiency of the enzyme pseudocholinesterase in some individuals)[1278a]

4 The well known precipitation of symptoms in acute intermittent porphyria by alcohol barbiturates, and other drugs[216–218]

5 The toxic methemoglobinemia that occurs in infants under the age of two months after exposure to either aniline dye-stamped diapers or to well water that is high in nitrate content (presumably due to the decreased concentration in the newborn s red blood cells of the enzymes necessary to reduce methemoglobin to hemoglobin)

6 The tolerance to atropine morphine barbiturates, and insulin in certain strains of animals (and presumably in certain humans) may well be related to their unique enzymatic detoxification mechanisms

Hypersensitivity mechanisms may also play roles of varying degrees of importance in rheumatic fever glomerulonephritis, erythema nodosum the dyscollagenoses the numerous infectious diseases which are associated with specific delayed type skin reactions idiopathic thrombocytopenic purpura and acquired hemolytic anemia For example, the association of

purple-fluorescing, vitiligo of the hands, and a sclerodermoid yellowing and hardening of the face and posterior neck are not infrequently observed in the adult form. The history of red hair turning dark or black, or gray hair darkening is also suggestive of this disease.[15, 20]

The cutaneous manifestations of hydroa aestivale, congenital porphyria, and mixed prophyria are pictured in Figures 15, 16, and 17 (Atlas pages 10 and 11), respectively.

In individuals having a latent inherited tendency toward porphyrinuria, the clinical syndrome may become evident following (1) the prolonged use of barbiturates, alcohol, and sulfonamides, (2) exposure of the skin to trauma, heat or sunlight, (3) toxicity from a variety of metals o organic compounds (TNT, CH_3Cl, CCl_4), (4) endogenous or exogenous progesterone,[216] or (5) another systemic disease, which precipitates it, particularly lymphoma, various blood dyscrasias, the avitaminoses, liver disease, and polyarteritis.[217, 218] It was observed that the diagnosis of a concomitant porphyria can be easily overlooked in cases of polyarteritis of the abdominal, polyneuritic, or polymyositic types. Since there are increased amounts of coproporphyrins in the urine in lead poisoning, and inasmuch as many of the symptoms of plumbism simulate those of porphyria, this differential diagnosis might merit considerable deliberation. It has been suggested that zinc ions may be responsible for an enzymatic block in porphyria and that chelation by means of BAL or EDTA is quite effective in the acute hepatic forms of the disease, especially when severe neuropsychiatric symptoms exist.[221]

Less emphasis need be directed to the much rarer and so-called erythropoietic form of porphyria. It is characterized by the abnormal production of uroporphyrins probably in the bone marrow. This genetic enzymatic defect in hemoglobin synthesis occurs most commonly in male infants or children. The full blown, clinical picture consists of photosensitivity, bullous-vesicular eruptions, hypertrichosis, red teeth, melanosis, red urine, a hemolytic anemia, and splenomegaly.

ALLERGY

There is little doubt that allergy to a wide variety of drugs, foodstuffs, infectious agents, pollens, dusts, danders, cosmetics and currently unknown factors can result in confusing syndromes involving multiple systems of the body. In fact the old maxim concerning the ability of syphilis to simulate most dermatologic entities can now be applied equally to drug allergy. One need only consider the fever, urticaria, bronchospasm, arthropathy, lymphadenopathy, nephropathy, polyneuropathy, and sterile meningitis following the use of penicillin, lipiodol or serum—which I have seen delayed as long as seven weeks—to appreciate this concept.

A brief enumeration of several manifestations of *drug allergy* will suffice to point out further the scope of this problem, which is cited in more detail under the chapter on iatrogenic disease (p. 384). These include (1) blood dyscrasias of all types (neutropenia, thrombocytopenia, aplastic anemia, leukemoid reactions),[3] (2) dermadromes of every description (morbilliform or scarlatiniform eruptions, urticaria, exfoliative dermatitis

paresthesias, and slurred speech The prolonged use of Bromo-Seltzer, B C headache powder, and bromide mixtures (Neurosine) is usually evident on careful history, but at times may be emphatically denied by the patient

Other features of bromism include fever, myalgia conjunctivitis, impotence, and arthralgia [2,9,230] In one out of four patients, various types of eruptions occur These consist of acneform lesions, erythema nodosum, erythema multiforme, urticaria, generalized exanthems, bullous and pemphigus like eruptions, and the more spectacular vegetative or granulomatous forms When it is present cyanosis is usually due to a concurrent acetanilid poisoning It should be borne in mind that the general physical condition of the patient often determines his susceptibility to the toxic effects of bromides Renal insufficiency, alcoholism general debility, arteriosclerosis, and desalting measures in congestive heart failure are commonly found as predisposing factors The level of the blood bromide at which signs and symptoms become manifest is highly variable, within a possible range of from 100 to 250 mg per cent (p 684)

The cutaneous manifestations of bromoderma are depicted in Figure 36 (Atlas page 23)

Salicylate poisoning (accidental therapeutic, or suicidal) may manifest itself as hyperpnea fever, hypoprothrombinemia eighth nerve and central nervous system signs, skin rashes and positive urinary acetone and ferric chloride tests Salicylic acid poisoning resulting from the use of this agent in dermatologic therapy is discussed under Group XIII (p 408) The initial respiratory alkalosis is later replaced by a metabolic acidosis One can readily appreciate how the aforementioned features—together with the frequently induced hyperglycemia, glucosuria, ketonuria polydipsia, and polyuria—could be readily confused with diabetic acidosis [231]

Chlorophenothane (DDT) is now being produced in greater tonnage than any other insecticide It can be constantly ingested in small amounts either from sprayed fruits and vegetables or from the fat of domestic animals used as meat Furthermore it is cumulative in human adipose tissue Intoxication may become manifest by marked sweating generalized tremors vomiting headache hyperexcitation spastic or flaccid paralysis and convulsions [2] Instances of cerebellar ataxia and neuronitis following exposure to the vapors of DDT and lindane have been reported [3 b]

Lead poisoning in adults is still a major problem wherever there are many old homes or industries in a community It should always be sought for in brass founding printing ceramics automobile body and storage battery workers, and in those using paints containing lead oxide There are frequently only vague gastrointestinal, central nervous system and muscular or neuritic complaints—with or without a mild anemia [233] Plumbism has even resulted from lead containing bullets and buckshot embedded in a serous cavity for a long time, or from the ingestion and retention of foreign bodies composed of lead in the gastrointestinal tract [234]

The manifestations of lead poisoning in the gums are depicted in Figure 38 (Atlas page 24)

The infrequency with which advanced chronic plumbism is encountered in the present era undoubtedly explains the rarity of saturnine gout

urticaria with other constitutional features should make one suspicious of disseminated lupus erythematosus The sprue like syndrome associated with wheat (gluten) sensitivity has already been mentioned (p 46) The variegated manifestations of vascular allergy, including the Henoch Schonlein syndrome, are discussed further under Group VIII (p 225)

The *Loffler syndrome*—or more descriptively, pulmonary infiltration with eosinophilia (the PIE syndrome)—is actually a nonspecific manifestation in a variety of diseases It is generally attributed to an allergic lobular and interstitial eosinophilic pneumonitis, without fibrin deposition, and with thrombosis of the small interstitial vessels The etiologic panorama has included penicillin reactions allergy states, hyposensitizing injections (especially for poison ivy) intestinal infestation, creeping eruption, bacterial and protozoal infections and the collagen diseases (most notably polyarteritis)[25]

Although most cases are undoubtedly of either an asymptomatic or a mild transient, and reversible nature the author has seen patients in whom a progressive chronic and even fatal course has ensued It is not unlikely that the present concept of the Loffler syndrome is too limited, inasmuch as gastrointestinal lesions serositis involving the pleural, pericardial and peritoneal surfaces, and infiltrations of the lymph nodes, epididymis and musculature have also been reported[26] Cutaneous lesions may be present, consisting of raised circinate plaques, vesicles, or bullae that can closely resemble erythema multiforme (Eosinophilic granuloma of bone with pulmonary manifestations is unrelated to this process)

THE POISONINGS

In light of the ready access of the general population to many powerful poisons both in industry and in the form of household agents, the number of cases of acute subacute and chronic poisonings which are never correctly diagnosed must be considerable There is another significant factor which contributes to this problem and frequently confronts physicians in the present era of mass advertising This factor is the replacement of the polypharmacy and complicated shotgun prescriptions of former years by the multitude of patent medications which are sold under numerous misleading trade names and can be readily purchased over drugstore counters In a review of the incidence of and mortality from the commoner toxic ingestants (excluding alcohol) at the Boston City Hospital there were 1457 patients admitted in a ten year period, of whom 97 died[28] Only some of the more important examples of poisoning as related to obscure illness will be discussed here

While the problem of *bromide intoxication* has been greatly reduced in recent years by the widespread use of the barbiturates and the "tranquilizers," it has by no means been eliminated Most of the reports pointing to the unexpectedly high frequency of this condition stem from studies of the blood bromide levels performed on all new admissions to those mental hospitals where the staffs were alerted to the neuropsychiatric manifestations of chronic bromide ingestion These consist of dizziness depression, confusion, memory loss hallucinations delusions nystagmus, diplopia

elaboration here The disease is so common, however, that a few additional remarks are in order Anasarca may be due to beri beri heart disease rather than the hypoproteinemia associated with malnutrition or cirrhosis of the liver Severe abdominal pain after an acute alcoholic debauch is commonly due to an acute pancreatitis rather than an acute gastritis One indication of acute pancreatitis as the cause of abdominal pain following bouts of acute alcoholism is the transient presence of a marked lactescence of the serum in these individuals [242] Physicians should avoid the temptation of labeling abnormal mental behavior or coma in an alcoholic as intoxication or alcoholic deterioration until thiamine deficiency, cerebral pellagra, various poisonings (including methyl alcohol) and an unrecognized subdural hematoma or skull fracture are ruled out

Alcoholism can also predispose to or accentuate the harmful effects of certain chemicals, drugs, and physical stresses, such as carbon tetrachloride poisoning, caisson disease [240] and hepatitis due to the arsenicals, cinchophen, and the sulfonamides There are many other metabolic derangements in chronic alcoholism, some of which may even be inadvertently aggravated by treatment The syndrome of *magnesium deficiency*—as manifested by gross muscle tremors, choreiform movements, convulsions, fever, sweating, and even delirium—is one case in point, since it usually follows prolonged parenteral fluid therapy This concept has considerable therapeutic potentialities in the management of both cirrhosis and delirium tremens [241]

A discussion of diagnostic problems caused by alcohol must include the problem of *methyl alcohol poisoning* This condition often closely simulates abdominal and cerebral emergencies [243] Whenever access to sufficient quantities of ethyl alcohol has been denied, particularly in skid row districts and in penal institutions the incidence of this serious disease has risen In fact during World War II, an alarming 6 per cent of all blindness in the armed forces was due to wood alcohol intoxication Not only may it ensue after a short latent period from ingestion of methanol in such forms as bootleg alcohol paint thinners, cheap hair tonics, inexpensive antifreeze preparations, varnish and shellac, but also from chronic exposure to its fumes during certain manufacturing and finishing processes Intoxication due to the ingestion of Solox—a paint solvent and shellac consisting primarily of ethyl alcohol and methanol—is seen with considerable frequency in the southern states [243d] This form of poisoning is characterized not only by the associated coma and acidosis but by the foul chemical odor of the breath and a concomitant severe hypoglycemia

Headache, dizziness, acidosis with Kussmaul breathing and loss of consciousness, convulsions mental disturbances violent epigastric pain (due to the pancreatitis) electrocardiographic abnormalities, and cardiovascular collapse have all been described from the ingestion of as little as one-half ounce [243e] Variable changes in the optic discs the retina, and the visual fields occur [244] The presence of fixed, dilated pupils indicates a poor prognosis The importance of differentiating these manifestations from a simple hang over and of promptly instituting alkali therapy is universally emphasized by all who have been interested in this disorder

This relative clinical familiarity with alcohol intoxication is not gen

an entity that was readily identified by clinicians during the last century It is probably comparable to the secondary gout occurring in other disorders of the hematopoietic system wherein there is an increased turnover of nucleoprotein [233b]

In an experience at a large naval shipyard during the recent war, the author found the quantitative test for urinary coproporphyrins to be an effective, rapid, and economical method for screening large numbers of exposed individuals for lead absorption In fact, coproporphyrinuria usually occurs earlier than the increase in stippled red blood cells (p 701) [235] The importance of detecting this condition in children as soon as possible is emphasized by a recent report of the profound emotional and intellectual deterioration which persisted in 14 out of 15 children who were studied for six months or more subsequent to this diagnosis [236]

Cases of possible poisoning by the *common solvents*, including the aromatic hydrocarbons, the chlorinated hydrocarbons, petroleum distillates, ketones, esters, alcohols, and carbon disulfide are frequent problems before the various industrial hygiene and compensation boards Several authorities have recently written of the potential hazards of even the so-called "safe solvents," such as methylene chloride and tetrachlorethylene [238a, b]

A transient exposure to *carbon tetrachloride* may result in nausea, vomiting, diarrhea, hepatic insufficiency, renal failure, heart failure, anemia, and hemorrhagic manifestations [237] It would appear that individuals who have inhaled carbon tetrachloride are more prone to experience an acute toxic nephropathy, whereas those who have ingested this substance tend to develop predominant liver injury [1800]

Poisoning due to the ingestion of *ethylene glycol* is apt to be occasionally encountered in view of the many new industrial uses of this compound, most notably in the manufacture of "permanent type" antifreeze solutions There ensues a characteristic evolution of the disease in the following three arbitrary phases, with death usually taking place at some time during the first two (1) central nervous system effects (within the first twelve hours)—stupor (resembling the effects of acute alcoholism), coma, convulsions, (2) cardiopulmonary effects (within the first twelve to twenty four hours)—progressive tachypnea cyanosis pulmonary edema, and (3) renal effects (beyond the second or third day)—flank pain and tenderness, proteinuria, anuria, *uremia, acidosis out of proportion to the degree* of uremia The nephrotoxic effect is probably largely the result of its metabolic product, oxalic acid Renal needle biopsy in these cases has shown the widespread epithelial cell necrosis and the deposition of calcium oxalate crystals in the tubular lumina [380]

Even *the synthetic detergents* are not innocuous This is evidenced by a fatality recently reported following the accidental ingestion of a small amount of a cationic detergent of the quaternary ammonium compound type [239] Inhibition of the essential enzymatic reactions connected with nervous function and intracellular oxidation was probably the mechanism of death Alcohol can potentiate the lethal effect

The effects of *chronic alcoholism* on the stomach, the liver, and the peripheral and central nervous systems are too well known to require

The cutaneous manifestations of arsenical dermatosis are depicted in Figure 37 (Atlas page 23)

The threefold increase in the arsenic content of American cigarettes over the past two decades is undoubtedly the result of the frequent spraying of crops with arsenic pesticides The potential public health hazards of such contamination are only now beginning to be appreciated It has been seriously suggested, for example, that the significant amounts of arsenic inhaled in the form of cigarette smoke, the detritus from the abrasion of synthetic rubber tires and tarred or oiled roads, and from the smoke and fumes of carbonaceous fuel combustion which pollute urban atmospheres might be etiologically related to cancer of both the tracheobronchial and genitourinary tracts [53a]

The most serious form of poisoning by arsenic however, is that due to *arsine* (hydrogen arsenide) which is an extremely poisonous gas that is formed whenever nascent hydrogen is liberated in the presence of trivalent arsenic This substance is probably the most powerful hemolytic agent encountered in industry and can result in a profound hemolytic anemia, hemoglobinuria and jaundice Most of these patients complain of severe nausea headache, and abdominal or costovertebral pain When one considers the numerous substances with which arsenic exists as a contaminant—such as zinc, lead, copper, antimony, gold, tin, silver, and the other recoverable ores—it becomes apparent that this type of poisoning should be sought out in unexplained illness affecting individuals who work with metals or acids [53b]

DIABETES MELLITUS

Diabetes mellitus has rightfully been referred to as ' the great imitator in modern medical practice Physicians in *all* fields would do well to pause occasionally and consider those manifold symptoms which should alert them to this common disorder as Moss has recently done [54]

The ophthalmologist—acute myopia cataracts in children and young adults retinopathy with microaneurysms retinitis proliferans Argyll Robertson pupils recurrent lid infections

The otolaryngologist—persistent xerostomia and dry throat recurrent pharyngitis

The cardiologist—coronary disease (particularly in premenopausal women) premature arteriosclerosis intercapillary glomerulosclerosis simulating heart failure early acidosis simulating functional heart disease postural hypotension (when the neuropathy affects the autonomic nervous system)

The chest physician—tuberculo is dyspnea due to early acidosis recurrent bronchitis and pneumonitis

The gastroenterologist—vague postprandial epigastric distress simulating gastritis and gastric malignancy carcinoma of the pancreas and chronic relapsing pancreatitis producing decreased glucose tolerance or frank clinical diabetes gallbladder disease hepatomegaly nocturnal diarrhea and fecal incontinence (with a neuropathy of the myenteric plexus)

The proctologist—constipation with hemorrhoids or rectal fissures due to the dehydration pruritus ani with or without a monilial infection

The urologist—polyuria nocturia urinary tract infections pruritus pudendae impotence paresis or atony of the bladder gram negative bacillus septicemia following instrumentation

The gynecologist—pruritus vulvae with or without a vulvovaginitis menstrual irregularities and amenorrhea sterility

erally the case with certain *toxic chemicals*, including mercury, arsenic, nickel, and cadmium. Most of these substances can produce various skin changes, chronic rhinitis, liver damage, peripheral neuritis, and bone marrow depression.[245] Several other chronic toxic effects of these chemicals when taken in the form of drugs are cited under Group XIII (p. 385).

Although mercury is no longer employed in this country in the felt hat industry (from whence the expression "mad as a hatter" originated), considerable quantities of metallic mercury are being used in the manufacture of fluorescent lamps, in temperature and pressure recorders, in miniature dry cell batteries for hearing aids, in electronic devices, and in various kinds of laboratory testing equipment. The use of turbines that utilize mercury vapor instead of steam will undoubtedly become more common with the harnessing of atomic energy for power purposes.[474] Such technological advances serve to underscore the increasing importance of a thorough occupational history in the presence of an obscure illness. About one third of the 4,000,000 pounds of mercury used annually in the United States is employed in the manufacture of agricultural chemicals. Another interesting illustration of this problem is the report of *mercury poisoning* in a number of policemen using a powder containing mercury for detecting latent fingerprints. Tremors, loosening of the teeth, and psychic irritability were encountered along with abnormally high urinary mercury levels.[247b]

A dirty slate-gray dermatosis has been noted with the topical use of mercurial agents, especially about the eyelids and facial folds. The percutaneous absorption of ammoniated mercury in generalized psoriasis and in other dermatoses has resulted in mercurial stomatitis.[243] Although admittedly uncommon, the possibility of mercurialism must be entertained when unexplained mental dullness, azotemia, gastrointestinal symptoms, and a severe gingivitis (with or without a blue-black mercury line on the gums) follow the prolonged oral ingestion of mercurial diuretics.[249] This response is usually unrelated to such idiosyncratic or allergic reactions to this group of drugs as chills, fever, leukopenia, thrombocytopenia, and cutaneous eruptions.

Whether accidental or the result of a homicidal attempt, *arsenic intoxication* poses a number of potential diagnostic problems. Even when there are few renal changes, the association of an acute necrotizing gastritis or jejunitis with radio-opaque material in the bowel is highly suggestive of acute arsenic poisoning.[250] The postmortem finding of tissue arsenical concentrations exceeding 0.04 mg. per cent is considered abnormal (p. 700).[31]

The possibility of an *arsenical neuropathy and encephalopathy* should be entertained in all patients with symmetrical nerve lesions who reside in rural areas where arsenical compounds are extensively employed as pesticides. A recent report of 41 cases observed in one North Carolina center re-emphasizes this consideration. The presence of associated gastrointestinal symptoms (particularly intestinal hemorrhage), hyperkeratotic scaling lesions (especially over the palms and soles), and transverse single white solid striae of the fingernails (Mee's lines) makes this diagnosis almost conclusive.[35] There is apparently a mobilization of melanin in arsenical intoxication that results in both hyperpigmentation and areas of depigmentation. The hyperkeratosis must be considered potentially premalignant in nature (p. 525).

The cutaneous manifestations of arsenical dermatosis are depicted in Figure 37 (Atlas page 23)

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The gynecologist—pruritus vulvae with or without a vulvovaginitis menstrual irregularities and amenorrhea sterility

The obstetrician—a high incidence of large babies stillbirths, premature deliveries neonatal deaths hydramnios, toxemias and cephalopelvic disproportions—even in the preclinical diabetic state (Avoid the potentially misleading diagnoses of "lactosuria and benign glucosuria" during pregnancy)

The pediatrician—acidosis and coma can occur very rapidly and may simulate other acute illnesses retarded growth thirst enuresis recurrent infections

The surgeon—recurrent skin abscesses cellulitis lymphadenitis, occlusive vascular disease with perforating ulcers and gangrene abdominal pain in acidosis simulating acute surgical crises

The orthopedic surgeon—nocturnal muscle pains in the legs, Charcot s joints (due to the neuropathy) perforating ulcers of the feet, osteomyelitis of the tarsal bones

The dermatologist—recurrent pyogenic skin infections vulvovaginitis pruritus *Candida albicans* infections especially of the fingernails and interdigital webs carotenemia xanthomata necrobiosis lipoidica, hemochromatosis

Xanthoma diabeticorum and necrobiosis lipoidica are depicted in Figures 11 and 12 (Atlas pages 8 and 9) respectively

The radiologist—premature calcification of the medium-sized arteries (especially in the legs or pelvis) calcification of the vas deferens multiple pancreatic calculi, neuropathic joints osteomyelitis of the tarsal bones

The endocrinologist—abnormal carbohydrate metabolism is encountered in many pluriglandular syndromes involving obesity menstrual disorders, impotence hirsutism acromegaly the Cushing syndrome thyrotoxicosis cachexia and pheochromocytoma it may also be deranged during steroid therapy

The neurologist—peripheral neuropathy autonomic nervous system neuropathy (postural hypotension impotence sweating disturbance Argyll Robertson pupils urinary bladder paresis nocturnal diarrhea) spinal cord involvement (neuropathic joints loss of vibratory and position sensation absent tendon reflexes) acidosis simulating cerebrovascular accidents uremia and alcoholism

The psychiatrist—simulation of functional neurotic or psychotic disease and organic brain damage due to both the diabetes and the associated accelerated cerebral arteriosclerosis

Experience has confirmed the value of the following observations in the clinician's attempt to diagnose correctly the presence of diabetes mellitus during its *silent biochemical phase*

1 Only by routine and repeated postprandial urine and blood tests for sugar can both the physician and the patient be assured of its absence, particularly if confronted with obesity and a strong family history of diabetes[253] It has been suggested that routine blood sugar determination may increase the number of known diabetic patients from 2 4 per cent to 4 per cent[256]

2 A formal or modified glucose tolerance test *must* be performed in *every* patient who has exhibited glucosuria, even only once (p 730) When retested, most patients with "nondiabetic glucosuria" prove to be diabetics

3 The most accurate times to check the postprandial effects of eating or of glucose loading are at one hour for the blood levels and at two hours for possible glucosuria (p 687)

4 A blood sugar level of 150 mg per cent should be the maximal level normally allowable after the ingestion of breakfast (a level still considerably less than the renal threshold)

5 In most instances of "preclinical" diabetes the fasting blood sugar is worthless

6 The renal threshold for sugar in patients with diabetes mellitus may have considerable clinical importance Insulin overdosage will occur if it is very low, while the dangers of uncontrolled diabetes exist if it is very

high The author has encountered one seriously ill elderly patient whose "threshold" ranged between 350 and 400 mg per cent (*vide infra*)

7 Although seemingly paradoxical at first glance, diabetes mellitus should be actively considered in individuals experiencing hypoglycemic episodes [89] Accordingly, they should be so treated if a diabetic-type glucose tolerance curve is found

8 Clinicians are usually so involved with the problems of diabetic management that the presence of melituria is almost automatically attributed to either true or renal glucosuria It must be borne in mind, however, that *fructosuria* is a likely possibility when melituria occurs in the presence of repeatedly normal glucose tolerance tests Such a situation calls for fermentation, resorcinol HCl, polarimetric, and levulose tolerance studies (p 705) [257]

9 Pregnancy, fever, infections, hyperthyroidism, and steroid therapy can all serve as "clinical glucose tolerance tests" in unmasking the hidden diabetic See Section XV of Part II for the provocative diabetic test with cortisone (p 827)

Several fine analyses of *the degenerative complications in diabetes mellitus* have appeared [258, 259] The combination of neuropathy, retinopathy and nephropathy has been aptly referred to as the "triopathy of diabetes" by Root and his colleagues, who have reviewed their extensive experience with this particular set of complications [260a] It is the general experience that the degenerative complications of diabetes mellitus do not occur in those forms of diabetes that are secondary to hemochromatosis, pancreatectomy, and other lesions

Asymptomatic gastric retention (gastroparesis diabeticorum) is a frequently overlooked manifestation of the diabetic (vagal) neuropathy It can adversely influence the treatment of the patient Similarly, it is important for the clinician to recognize the possibility of an atonic neurogenic bladder resulting from a "sensory paralytic bladder" in patients with long standing diabetes mellitus who are experiencing nocturnal incontinence or prolonged intervals between micturition [55b]

One should bear in mind that a mistaken clinical diagnosis of the Kimmelstiel Wilson syndrome may be made in the diabetic patient if it is based solely on the presence of hypertension, albuminuria edema, and retinopathy On many occasions, these findings are actually associated with pyelonephritis or nephrosclerosis alone [261]

Studies dealing with the absorption and excretion of radioactive vitamin B_{12} in diabetic patients, both with and without complicating neuropathies and retinopathy, affirm the clinical impression that there is an impairment in the absorption and metabolism of this vitamin [60b] The pathogenetic prophylactic, and therapeutic implications of such observations with reference to diabetic complications are considerable

A number of important considerations might confront the consultant asked to see a patient with *severe diabetic acidosis responding poorly to therapy*

1 *Ketosis and acidosis may follow protracted periods of insulin hypoglycemia* in the absence of an adequate supply of exogenous carbohydrate

Hyperglycemia, glucosuria, ketosis, and resistance to insulin can actually represent starvation phenomena due to the depletion of hepatic glycogen This is particularly prone to occur in the juvenile diabetic, the "unstable" adult, and the patient who is vomiting Such a situation calls for a reduction (rather than an increase) in the insulin dosage [26]

2 *Infection or visceral inflammation* must always be sought out and vigorously treated in *every* unexplained case of diabetic acidosis Renal tract infection gastroenteritis localized abscesses pneumonitis, myocardial infarction, and endocarditis are most apt to result in this type of difficulty Acute appendicitis could be very misleading (and even fatal) under these circumstances [263a]

3 Harmful *hypernatremia* may be induced by (1) the overzealous infusion of isotonic saline solution, especially in excess of 4 liters in twenty four hours,[264] and (2) the failure to include in a consideration of the patient s electrolyte status the effective osmotic pressure exerted both by marked elevations of the blood glucose and by the hyperlipemia Since 36 mg per cent of excess glucose will exert an osmotic pull on the cells equivalent to 1 mEq of sodium chloride, a serum sodium of 140 mEq per liter in the presence of a blood sugar of 360 mg per cent might be actually misleadingly low by 10 mEq per liter [265] The use of hypotonic salt solutions is desirable since in most instances there is a greater deficiency of water than of salt The dangers of hypernatremia are accentuated when marked potassium depletion also exists [265b]

4 Similarly, a serious *chloride acidosis* may result from the administration of excessive amounts of chloride [265c] It is recalled that the normal concentration of chlorides in the extracellular fluids approximates 100 mEq per liter, in contrast to the 150 mEq per liter found in isotonic "physiological" saline solution

5 The serious effects of *hypopotassemia* (extreme weakness, collapse, heart failure) must be anticipated Since the heart tenaciously retains its electrolytes a close correlation between the serum potassium levels and electrocardiographic changes is not always present Furthermore, inasmuch as acidosis tends to increase the level of the serum potassium independently of the intracellular potassium stores a normal serum concentration in the presence of severe diabetic acidosis may represent significant depletion of this electrolyte [266] Although fructose is more effective than glucose in reducing hyperglycemia it increases the urinary losses of both potassium and sodium [267] The great temptation to administer large amounts of potassium following diabetic coma that is prevalent in many quarters should be discouraged, since rarely is hypokalemia a problem before ten or twelve hours By that time by far the majority of these patients should be able to take potassium rich nourishment by mouth

6 *Anuria* may be due to bilateral and symmetric necrosis of the renal cortices It would be almost superfluous to point out that the presence of a blocked catheter can be misconstrued as anuria, were it not for the fact that most clinicians have encountered this embarrassing problem The serious hazards attendant upon catheterization in the diabetic when not absolutely mandatory—even in the presence of a lower nephron nephrosis '—will be repeatedly emphasized throughout this book

7 *Abdominal pain* may be produced in the diabetic (or in the normal subject) who is being infused with *fructose solutions* at a relatively rapid rate [67b]

8 When in doubt concerning the significance of unusual clinical manifestations in a patient with diabetic precoma or coma the clinician must continue intensive treatment during the ensuing period of observation Some of these features could include *intensive lumbar pain acute abdominal pain, maniacal restlessness and violence, epileptiform convulsions, and deepening unconsciousness* during treatment [68] The unconsciousness may be profound (twelve to twenty four hours), yet bearing no relationship either to hypoglycemia or to hypokalemia If a patient becomes unconscious after several hours of doing well following treatment for diabetic acidosis, an immediate recheck of the plasma ketones by the simple technique of Duncan might be of inestimable value in determining the presence of either acidosis or hypoglycemia (It is not infrequently observed that ketone bodies can persist in the urine after adequate therapy, even when they have disappeared from the plasma)

9 *Recurrent coma* in the diabetic that is associated with severe renal disease acidosis, and hyperglycemia but without ketonuria, also makes the determination for ketonemia almost mandatory (This test can be readily performed at the bedside by adding one drop of plasma or serum to an "Acetest ' (Ames) tablet) When ketonemia is absent the coma is probably due to a combination of renal failure chronic pyelonephritis, and the *diabetic nephropathy* [263b]

10 A further brief elaboration is in order pertaining to those discrepancies that are occasionally encountered wherein *the urine fails to reflect the high blood levels of both glucose and the ketone bodies* This can be explained to a large degree by the currently evolving concept that there is actually *no* specific threshold concentration at which these substances predictably appear in the urine The presence or absence of glucosuria depends first on the glucose load that is presented to the kidney tubules, and secondly on their capacity to absorb this load Even with very high blood sugar levels little or no glucosuria may appear if the filtration rate or tubular activity is reduced as a result of renal disease dehydration, sodium depletion or combinations of these factors

11 The author has recently begun to encounter instances of acidosis or near acidosis among conscientious diabetic patients Further investigation has shown that these individuals were being misled as to the degree of their glucosuria by their switching to the use of the *paper enzyme tests* for the determination of urinary sugar Others have also been impressed with such *erroneous quantitative results* especially when the glucose concentrations exceeded 0 1 per cent [263b]

12 *It is not only possible for hyperthyroidism to reveal a latent* diabetes mellitus but also for *a thyrotoxic crisis to precipitate a diabetic ketoacidosis* [40c d] This situation is most apt to arise when antithyroid medication (especially the iodides) is either withdrawn or stopped before adequate control of the Grave s disease has been achieved After control of the latter disorder the diabetes mellitus will usually revert to its prior status

13 *Insulin resistance* must be considered in individuals who require

extraordinary amounts of insulin for control, i e, usually above 200 units per day Some of these patients also exhibit evidence of insulin allergy There is ample support for the contention that such resistance in many instances is the result of the development of specific antibodies[266a] In fact, corticotropin has had favorable results in some of these cases[266b] In the majority of instances of insulin resistance, however studies for abnormalities in the thyroid, adrenal cortex or pituitary, liver dysfunction, and neutralizing antibodies to insulin reveal nothing

Recent studies relating to the nature of insulin binding antibodies have begun to cast considerable light on the nature of insulin resistance[266d] Exogenous insulin becomes bound by certain serum globulins (specifically, those just in advance of the gamma globulins by electrophoretic studies) In effect, these globulins represent the development of antibodies to this hormone after it has been given for several months It is possible that the antigen is derived either from some animal protein component (there are a total of eight possible different mammalian insulins presently available) or some change in the insulin molecule itself which takes place during the extraction of insulin As a result of the formation of this insulin antibody complex, insulin is "sequestrated" and protected from the action of the hepatic enzymes

In instances of insulin resistance, the titers of the antibody may be so high that the rapidity of the insulin binding virtually precludes the escape of free insulin into the tissues (Serum from patients who are insulin resistant is known to bind from 80 to more than 500 units of insulin per liter of plasma) Tremendous quantities of insulin are needed to saturate this binding capacity of the serum in treating these cases By the same token, however, the patient runs the risk of subsequent hypoglycemic reactions due to the slow release of insulin from the large amounts of the dissociating complex in the tissues It appears likely that the beneficial effect of the adrenal steroids in cases of insulin resistance is related to their effect upon the insulin binding antibody

OTHER "ERRORS OF METABOLISM"

Gout

Hyperuricemia and gout can no longer be said to affect only the joints Serious cardiac and renal involvement may also occur Furthermore, there is an associated increased incidence of degenerative vascular complications, diabetes mellitus, leukemia polycythemia, and Paget's disease[69, 70] The primary nephropathy is a direct effect of the uric acid crystallization and deposition whereas the secondary forms of the gouty kidney result from both the sequelae of the primary changes and the accelerated vascular degeneration In "gouty nephrosis" there is characteristically little or no albuminuria or changes in the sediment

The cutaneous manifestations of gout are depicted in Figure 61 (Atlas page 32)

The problem of distinguishing gout from rheumatoid arthritis occasionally presents itself under the following circumstances (1) gout can at times closely simulate rheumatoid arthritis, (2) a proportion of patients

with rheumatoid arthritis have hyperuricemia in the absence of clinical gout, and (3) rheumatoid arthritis and gout may coexist in the same individual The value of synovial biopsy with fixation of the tissues in absolute alcohol for demonstrating the acid urate crystals is discussed in Section XI of Part II (p 800)

The precipitation of an arthropathy by mercurial diuresis, liver or bile salt therapy, trauma, or immobilization is occasionally the first clinical clue to the presence of gout [270d] The local cutaneous desquamation following an attack is also helpful in directing attention to this disease Clinical sensitization to probenecid (Benemid) aptly called "the insulin of gout," may occur infrequently in the form of pruritus, generalized urticaria, other drug rashes, drug fever a marked eosinophilia, and severe or even fatal myocarditis and massive hepatic necrosis [271] Desensitization has been successfully achieved [271d]

Radioisotope studies have recently shown that the *secondary gout* which results from various hematopoietic disorders (most notably primary and secondary polycythemia myeloid metaplasia and leukemia) is in all probability not due to the precipitation of an underlying gouty trait Rather it represents the incidental result of nucleic acid synthesis from more indirect metabolic pathways An example of the different predominant pathways of uric acid biosynthesis is found in the sharp contrast between the rapid peak of glycine-N^{15} incorporation into uric acid in primary gout as contrasted with the slow peak in secondary gout [72]

Ochronosis

Ochronosis occurs in about half of those afflicted with hereditary alkaptonuria It is usually identified by the blackening of the urine on exposure to air in patients with a severe peripheral arthritis or an ankylosing spondylitis and by the dark staining of the underclothing from urine and perspiration It may be confused with diabetes mellitus due to the presence of a reducing substance in the urine The skin in ochronosis exhibits a mottled brown or blue pigmentation about the neck head torso extremities, axillae and genital areas A bluish color of the ears or a gray-blue discoloration of the sclerae often represent the only external pigmentation [15] Lichtenstein and Kaplan have emphasized that serious cardiovascular involvement can occur in the form of severe arteriosclerosis and pigment induced stenosis of the aortic and mitral valves [273] Nephrosis, deposition of pigment in the pancreatic islets and the formation of pigment calculi in the urinary tract can also develop [274]

The ocular manifestations of alkaptonuric ochronosis are depicted in Figure 49 (Atlas page 31)

Galactosemia

Although it occurs infrequently galactosemia is briefly mentioned for one reason namely the potential regression or disappearance of the features of this disorder by elimination of galactose (milk) from the diet of infants These include mental retardation cataracts galactosuria azote

mia, proteinuria, anemia, hepatosplenomegaly and ascites This interesting syndrome apparently results from the congenital absence of the specific enzyme, P Gal transferase, the absence of which has been readily diagnosed in red blood cells subjected to spectrophotometric analysis[275]

THE GLYCOGEN STORAGE DISORDERS

There are a number of variants that comprise the glycogen storage disorders These rather rare conditions represent a complex derangement of the carbohydrate metabolism involving both the structure of the glycogen and enzyme deficiencies They occur in infant siblings and are manifested by abnormal glycogen storage in the body[8, 90, 4] Accordingly, the stored glycogen is no longer available for the metabolic needs of the body in the form of glucose

The following brief review of the three chief variants points out the clinical ramifications of this metabolic defection

1 The *hepatic type* (von Gierke's disease)—characterized by an inability to maintain weight and growth, hepatomegaly anorexia, apathy, and convulsions or coma stemming from the hypoglycemia In addition to the fasting hypoglycemia, there is acetonuria a prolonged glucose tolerance curve and decreased glycogen response to epinephrine and glucagon A subvariant includes cirrhosis formation In this type, the hepato plenomegaly and ascites are not accompanied by hypoglycemia acidosis, or abnormal glucose tolerance curves

2 The *muscular type*—characterized by a progressive muscular weakness simulating amyotonia congenita The deposits of glycogen are found chiefly in the striated muscle and to a lesser extent in the liver kidneys and heart

3 The *cardiac type* ('cardiomegalia glycogenia')—*characterized* primarily by a markedly enlarged heart with a globular configuration and secondary compressive and atelectatic pulmonary changes Hepatomegaly is infrequent, and a palpable spleen or kidneys even less common The various blood and urine chemistries that have been recorded in these patients are normal This condition and others which can result in hypertrophy of the infant heart are considered in a later chapter (p 232)

THE DISORDERS OF LIPID METABOLISM

When confronted with the presence of unexplained yellowish cutaneous plaques the clinician should accept the challenge of ruling out or ascertaining the presence of an underlying systemic illness such as diabetes mellitus cirrhosis myxedema Gaucher's disease, elastica disease and hypercholesterolemia The xanthic lesions are discussed at further length under Group XVII (Cutaneous Medicine, p 521) Thannhauser's book and reviews of the lipoidoses are valuable references on the subject[78]

The normocholesterolemic granulomatous reticuloendothelioses, including the Hand Schuller Christian syndrome and eosinophilic granuloma, are usually unrelated clinically to the lipoidoses These entities are discussed under Group VII (p 207) Occasionally however, a case is encoun

tered in which the high serum lipid content, the hypercholesterolemia, the osteolytic lesions, and the histologic finding of lipid granulomas appear to bridge the gap of the hypercholesterolemic, hyperlipemic, and normocholesterolemic syndromes[286]

Xanthomatosis

There is a variety of morphologically unique *xanthomata* including xanthelasma xanthoma tuberosum xanthoma disseminatum and the so-called eruptive type The last occurs in diabetics frequently starting as small glistening papules which resemble tense vesicles The eruption may spread extensively to affect the trunk extremities and mucous membranes as yellowish or reddish brown nodules In the case of *xanthoma tuberosum*, the biliary tract the cardiovascular system the spleen and the lymph nodes are commonly infiltrated as well as the skin and tendon sheaths A number of cases of juvenile heart disease have been observed in hypercholesterolemic xanthomatosis as evidenced by myocardial infarction endocardial and valvular involvement and sudden death in children[277, 278] *Xanthoma diabeticorum* fluctuates with both the levels of the serum lipids and the course of the underlying diabetes It consists of purplish red papules with yellow centers and has a predilection for the extensor aspects and the palms and soles

Xanthoma tuberosum and xanthoma diabeticorum are pictured in Figures 10 and 11 (Atlas page 8) respectively

Essential Familial Hypercholesterolemia

It has been demonstrated that essential familial hypercholesterolemia is transmitted as a dominant characteristic but that the occurrence of xanthomas is dependent largely upon the level of the serum cholesterol[279] Whereas hypercholesterolemia without xanthomatosis (latent xanthomatosis) is the rule in children and young adults, a progressive xanthomatosis will subsequently develop in at least 80 per cent The presence of a primary 'forme fruste' hypercholesterolemia should be suspected in obscure cases of coronary occlusion particularly in young females and when thrombotic phenomena follow the institution of steroid therapy[80] Perhaps dietary and pharmacologic prophylactic measures in asymptomatic individuals with this disorder—usually discovered among the relatives of patients with cardiovascular disease by interested physicians—may serve to avert or to delay its serious sequelae

Essential Hyperlipemia

Essential hyperlipemia is a less common familial disorder that is characterized by a pronounced elevation of the total blood lipids particularly the neutral fat component (which causes the serum to appear creamy) In contrast to the normal levels of 500 or 600 mg per 100 ml for the total lipids levels as high as 12 400 mg (or 12 per cent) are on record in patients with essential hyperlipemia (This figure assumes even greater impressive-

ness when one realizes that the fat content of cream is 30 per cent) There may be cutaneous xanthomatosis, lipemic retinitis, hepatosplenomegaly, and severe abdominal pain[281] Although the abdominal crises are attributed to many factors (xanthomatous or atherosclerotic lesions in the pancreas and other viscera, lipid particle embolization, and neurologic changes), they have not been satisfactorily explained

In contrast to familial hypercholesterolemic xanthomatosis, essential hyperlipemia usually has a relatively good prognosis In general, there is little tendency towards premature arteriosclerosis When associated with diabetes mellitus, however severe vascular damage may be found[282] The *ill appearance of the patient, the failure of diet alone to reverse the xanthomata*, and the correction of the hyperlipemia by diabetic management serve to distinguish xanthoma diabeticorum from idiopathic hyperlipemia, with or without an associated diabetes mellitus

The basic metabolic defect in familial hyperlipemia is probably an en*zymatic defect or deficiency involving lipoprotein lipase, which retards the* removal of ingested fat from the blood stream after normal absorption This is usually the only overt derangement in the heterozygote abnormal state, and can be demonstrated by a fat tolerance test as is described in Section XVI of Part II (p 827) The correctness of this concept is shown by the reduction of the existing hyperlipemia and the secondary elevation of the cholesterol and phospholipids following both rigid fat restriction and the proper spacing of fat feedings[283] It should be appreciated that the serum may exhibit little evidence of opalescence, particularly in the case of the younger patients If the blood cholesterol is the only lipid determination which is readily available, it might be difficult to differentiate this condition from essential familial hypercholesterolemia Fat restriction *per se* has little or no effect on the latter lipid derangement

Lipoid Proteinosis

The few reported cases of lipoid proteinosis have been usually free of serious generalized involvement and elevated blood lipids[284] The disorder is characterized by the appearance of white or yellow plaques and nodules in the skin (particularly the face, elbows, and knees) and mucous membranes Hoarseness may result from the vocal cord involvement and parotitis from the obstruction to Stensen's duct Its association with diabetes mellitus and a familial occurrence have also been noted Thannhauser has described epileptic seizures in this condition[2 5] While he favors the opinion that lipoid proteinosis is the late fibrotic phase of eosinophilic xanthomatous granuloma (the Hand Schuller Christian syndrome), others do not feel that it represents a true xanthoma Lipoid proteinosis is described under a variety of other terms, most notably *hyalinosis cutis et* mucosae It is regarded by some as a genodermatosis which is familial, and possibly related to consanguinity[285b]

Gaucher's Disease

Gaucher's disease, a chronic familial disease characterized by the deposition of kerasin in the cells of the reticuloendothelial system, can be

confusing for long periods because of its many subtle clinical manifestations Hepatosplenomegaly, pinguecula, anemia refractory to treatment, leukopenia, thrombocytopenia with a hemorrhagic tendency, painful bone changes, and pathologic fractures may occur[287] The vertebrae, femora, and tibiae are the bones most commonly affected An uneven, brownish tan pigmentation occurs in approximately one half of these patients, especially on the exposed parts Mucous membrane involvement is not usually found in the absence of adrenal infiltration by the Gaucher cells Splenectomy and preoperative cortisone have temporarily benefitted the associated hypersplenism in some patients[288]

The ocular manifestations of Gaucher's disease are depicted in Figure 97 (Atlas page 63)

A study of the bone marrow and x rays of the lower femora are often diagnostic (pp 677 and 804) The clinician may occasionally be rewarded by considering the possibility of Gaucher s disease in the patient with an apparently normal prostate or with benign hypertrophy of this organ who is found to have a very high titer of serum acid phosphatase (up to 10 3 Gutman units in one report)[289] In this situation, the hepatosplenomegaly and the degree of disability are apt to be minimal

THE SPECIFIC ELECTROLYTE DEPLETIONS

The subject of the specific electrolyte depletions and excesses has received considerable (and at times exaggerated) attention during the past decade This emphasis has resulted from the improvement and increasing availability of the flame photometer technique along with various diets and therapeutic regimens that can readily induce these states in susceptible individuals The reader is referred to other discussions in this book dealing with iatrogenic electrolyte disturbances that may be encountered postoperatively (p 474) and in the treatment of diabetes mellitus (p 71) and congestive heart failure (p 246) A brief review of the flame photometer technique (p 696) along with an analysis of the normal and abnormal concentrations of the serum and urine electrolytes so determined can be found in Sections II and III of Part II

The fatal respiratory paralysis following treated diabetic coma, the enhancement of digitalis intoxication, the "medical ileus in the partially obstructed ulcer patient, and the loss of potassium both via the urine (in chronic renal disease) and the bowel (in diarrhea or with the excessive use of laxatives and enemas) serve to underscore the many aspects of *potassium depletion*[291 95]

Serial electrocardiographic tracings sometimes aid in the diagnosis and treatment of deranged potassium states The most significant findings in hypopotassemia are U waves greater than 1 mm in amplitude and S T depressions of more than 0 5 mm While disturbances in the concentration of the other plasma electrolytes or the pH of the blood do not usually prevent the development of these signs they may be obscured by the lengthened Q T interval in hypocalcemia or by the merging of the P waves with U waves of decreased amplitude in the presence of a tachycardia

The decreased activity of the deep tendon reflexes is actually the

only clinical sign that shows significant correlation with the decrease in plasma potassium levels[291d] When it is difficult to decide whether certain signs and symptoms are due to potassium depletion, one might observe the changes following the rapid infusion of potassium, especially with reference to improved mental function and increased peristaltic activity

While the serum potassium concentration is usually an accurate guide to the status of this electrolyte in most patients, there are many homeostatic and pathologic influences constantly at play that influence the total potassium content and capacity These must be taken into consideration by the clinician in estimating the degree of depletion or excess With reference to acid base disturbances, for example it has been demonstrated that acidosis increases and alkalosis decreases the concentration of serum potassium independently of the intracellular potassium stores[296] Thus, a slight decrease in the serum concentration of potassium in the face of a severe alkalosis is probably not significant, whereas even a normal initial level is suggestive of significant depletion if a severe acidosis exists

Many patients described as having a "potassium losing nephritis," may in reality have had primary aldosteronism (p 29)[94] One can usually differentiate the effects of primary potassium depletion from hyperaldosteronism by the decreased potassium in the urine, the normal serum sodium and the acidity of the urine associated with the former state Unfortunately the situation in primary aldosteronism may be complicated by the secondary renal changes stemming from the profound hypokalemia

The depletion of potassium by diarrhea in a patient with prolonged nutritional deficiency (sprue pellagra ulcerative colitis) can also result in both a diffuse vacuolar nephropathy with marked renal insufficiency and acute degeneration of skeletal muscle even though dehydration sodium depletion and significant acid base disturbances are absent[297, 298] Following appropriate therapy rapid clinical recovery has been noted This nephropathy is not limited to the diarrheal diseases, however but can become a significant counterpart of hyperadrenalism (cortisone or aldosterone effects) and renal potassium wasting (as in the Fanconi and tubular acidosis syndromes) in both of which instances significant amounts of potassium may be found in the urine

The occurrence of attacks of weakness or paralysis during the middle of the night or following the ingestion of carbohydrates is highly suggestive of familial periodic paralysis[299] Similarly, in patients on the verge of clinical digitalis toxicity the reduction of the blood potassium by oral or intravenous carbohydrate has precipitated various ventricular arrhythmias[300] This suggests that patients receiving large doses of digitalis should be placed on a high protein and low carbohydrate diet, supplemented by potassium salts

The clinical and therapeutic problem is equally important in the case of *sodium depletion* variously caused by the chronic excessive loss of this ion in the sweat or urine, following paracentesis or produced by vigorous diuresis and other factors in the treatment of heart failure[303] It is quite significant in some cardiacs to know whether a given electrolyte disturbance is due primarily t[illegible] loss of the sodium ion or the chloride ion (hypochloremic [illegible] of the more satisfactory therapy and better prognosis a[illegible] latter state[304]

The precipitation of a low sodium syndrome following pulmonary infarction in a number of patients whom my colleagues and I observed has been most impressive. A 'salt losing nephritis' should be suspected in those cases diagnosed as "Addison's disease with hypertension" (p. 52).[2, 3, 179] Sodium losing syndromes have also been noted in the presence of apparently normal kidneys and adrenals in certain patients with pulmonary and meningeal tuberculosis, and with pulmonary, mediastinal and central nervous system tumors.[305a] Instances are on record in which patients with disseminated malignancies (most often a bronchogenic carcinoma) have demonstrated marked and progressive hyponatremia concomitantly with a persistent loss of sodium in the urine in spite of the progressive plasma hypotonicity.[305b] Inasmuch as these patients were found to have apparently normal renal and adrenal function (and were also noted to have grossly and microscopically normal pituitary glands), this unusual situation could be explained by a sustained and inappropriate secretion of antidiuretic hormone along with an expanded body fluid volume.

Orthostatic hypotension in a young adult should raise the possibility of an underlying sodium depletion. It is not generally appreciated that sodium deficiency may be manifested by hypovolemia rather than by hyponatremia. There are many patients who are seriously ill from a variety of causes in whom an unexplained severe hyponatremia develops that bears no overt relationship to salt loss. Asymptomatic hyponatremia (or asymptomatic hypotonicity) is apt to be encountered in patients with chronic wasting illnesses and after parenteral fluid therapy has been given over long periods of time. In this group the administration of saline might even be detrimental and should be carried out only after the greatest deliberation (p. 248).

Isolated *magnesium deficiency* as the cause of confusion, stupor, tremors and athetoid movements has been documented in patients with profuse diarrhea who are given prolonged parenteral fluid therapy without this electrolyte and in whom the potassium and calcium levels are not remarkable.[241] Reference was made earlier to the possibility of this syndrome when these features are noted during the management of patients with chronic alcoholism and delirium tremens (p. 67).

THE SPECIFIC ELECTROLYTE EXCESSES

Unsuspected electrolyte excesses that may confuse the clinician are less common, but it is equally vital to diagnose them correctly. The possibility of inducing a severe *hyperchloremic acidosis, hyperkalemia* or *ammonium intoxication* by the prolonged administration of ammonium chloride or potassium preparations in the presence of renal and hepatic disease is apparently considered only infrequently in diuretic therapy.[306] It is not unlikely that more instances of 'pure' hypoaldosteronism will be suspected when symptomatic hyperkalemia (most probably in the form of Stokes-Adams attacks) is encountered in association with a minimal excretion of aldosterone in the urine, particularly in association with a low sodium diet.[9]

Symptoms of weakness, fatigability, anorexia, weight loss, a salty taste and nausea with vomiting following radical bladder surgery and

only clinical sign that shows significant correlation with the decrease in plasma potassium levels[291d] When it is difficult to decide whether certain signs and symptoms are due to potassium depletion one might observe the changes following the rapid infusion of potassium, especially with reference to improved mental function and increased peristaltic activity

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because of photophobia and the abnormal light diffusion ("I have to read between the spots") The special importance of the corneal calcification is that it may be the only definite evidence of previous hypercalcemia once secondary renal damage—with the concomitant lowering of the serum calcium level—has taken place

An even more frequent site of calcium deposition is on the eyelids under the tarsal ridge

The ocular manifestations of hypercalcemia are depicted in Figure 47 (Atlas page 29)

Pediatricians in the larger medical centers are becoming more aware of the disorder referred to as *idiopathic hypercalcemia* This condition might actually represent a state of hypersensitivity to vitamin D[315] The diagnosis may be suggested by the patient's elfin like face, the marked muscular weakness, anorexia, vomiting constipation, failure to thrive and mental retardation The roentgenographic findings are rather distinctive, consisting of an amorphous increase in the density of the skull and the epiphyses transverse bands of increased density at the ends of the bones, faulty tubulation and deposition of calcium in the kidneys and other soft tissues

It is equally important to take cognizance of the possibility that "idiopathic hypercalcemia of infancy, with failure to thrive may represent excessive consumption of vitamin D If one tallies the total amount of this vitamin that is given to infants in the form of fortified milk bread, commercial formulas infant cereals, and supplementary vitamins (particularly in the all too common vitamin hysterical environment), it becomes apparent that much more is being consumed than the recommended dose of 400–800 international units daily[315b]

bilateral ureterosigmoidostomy are frequently due to a *hyperchloremic acidosis and hypokalemia* [307] This is primarily the result of the excessive resorption of chloride from the rectal mucosa Fortunately, it can be very readily treated once recognized The occurrence of cardiac arrest or defects of intraventricular conduction in the presence of only moderate elevations in the serum potassium should alert the clinician to the possibility of an associated hypocalcemic state

Even more subtle are the *hypernatremia and hyperchloremia* associated with azotemia following prolonged nasogastric tube feeding, due to the excessive protein intake and dehydration [308] Hypernatremia and hyperchloremia may also be secondary to lesions in the region of the hypothalamus and third ventricle [309] It appears likely that the hypernatremia, hyponatruria hyperkalemia azotemia, and acidosis which develop in the comatose patient who has sustained a severe injury to the brain represent a normal physiologic response to the severe water deficit resulting from such factors as fever, sweating, and hyperventilation [309a] In patients whose potassium stores have been greatly depleted (as in the case of diabetic acidosis) a serious excess of sodium in proportion to potassium can be readily produced by the infusion of excessive intravenous sodium [264] The problem of *orthostatic hypernatremia* will be discussed under the subject of "refractory' heart failure (p 231) [310]

The several important causes of *hypercalcemia* (hyperparathyroidism, hypervitaminosis D, the milk alkali syndrome, acute osteoporosis, sarcoidosis, immobilization of patients with Paget s disease, myelomatosis) are discussed elsewhere under their appropriate groups (pp 23 205, 403 and 406) Attention is also directed to the occurrence of hypercalcemia—defined as a calcium level in excess of 12 mg per 100 ml of blood—in generalized carcinomatosis with osseous metastases This is particularly significant when estrogens are used in the treatment of metastatic disease of the breast [311] In several instances, the hypercalcemia appears not to have been dependent upon bone metastases or destruction but upon substances introduced into the circulation by the tumors, which in turn produced bone resorption [312] While it occurs much less frequently in Hodgkin's disease than in carcinoma metastasizing to bone hypercalcemia of striking proportions has been encountered in the former disease [316] These patients may be much more prone to the toxic effects of vitamin D a situation analogous to a similar hypersusceptibility in sarcoidosis

The diverse clinical manifestations of hypercalcemia are referable to the central nervous system, the autonomic nervous system, the kidneys (polyuria is very prominent), the gastrointestinal tract, and the cardiovascular system [313] While convulsions are more often a sign of hypocalcemia it appears that previously latent cerebral metastases can become manifest clinically in some patients during periods of hypercalcemia

There are several interesting and diagnostic features of hypercalcemia in the conjunctival and corneal tissues both clinically and radiographically [314] The ocular calcification might resemble arcus senilis to the naked eye except that it is most prominent at the medial and lateral margins of the cornea, the band keratopathy is patchy, and there is a clear rim adjacent to the sclera Many of these patients first consult an eye specialist

GENERAL CONSIDERATIONS IN THE DIAGNOSIS OF LIVER DISEASE

IN ANY TREATISE that deals with the problem of obscure disease, considerable emphasis must be placed upon the diagnostics of the subacute and chronic phases of hepatitis and cirrhosis, particularly in the absence of jaundice and ascites. Both of these conditions are very common and undoubtedly account for much prolonged undiagnosed illness if the physician is not "liver conscious." For example, a postnecrotic cirrhosis is not infrequently found at autopsy in patients whose clinical course gave no hint to the possibility of liver disease.[317a]

In addition to diabetes mellitus and several other metabolic diseases that were discussed under Group II, reference is repeatedly made throughout this text to the significant hepatic pathology encountered in a host of unrelated disorders. These include neoplasms, abscesses, the granulomatous and collagen diseases, infections (leptospirosis, amebiasis, tuberculosis, brucellosis, schistosomiasis, echinococcosis), the lymphomas and the leukemias. Gall and Landing have reviewed a number of genetically determined metabolic disorders that lead to cirrhosis of the liver with varying degrees of severity. These include Wilson's disease, galactosemia, the glycogen storage diseases, gargoylism, Gaucher's disease, Niemann-Pick's disease, cystinosis, and hemochromatosis.[31b] The subject of nonparasitic polycystic disease of the liver is commented upon under Group XIV (p. 424).

PHYSICAL DIAGNOSIS

It is not amiss to remind the reader of several important but commonly neglected considerations in the physical diagnosis of liver disease. First, clinicians who pride themselves on their ability to detect minimal jaundice universally attest to the importance of adequate natural light. The absence of pigmentation of the eye in a suspected case of jaundice should direct the clinician's orientation along other lines, such as carotenemia and atabrine pigmentation (neither of which produces a van den Bergh reaction). It should be axiomatic that children and adults below the age of thirty years with unexplained cirrhosis be subjected to slit lamp examination for the Kayser-Fleischer ring, particularly if intermarriage exists in the family.

The skin must be closely observed not only for spider angiomas and anemia, but also for xanthelasma and the cutaneous xanthomas (p. 525). These dermadromes may be the first and only clinical findings in the so-called xanthomatous biliary cirrhosis.[318] Increased melanin pigmentation is occasionally quite pronounced in cirrhosis, particularly on the exposed surfaces; this is considered a poor prognostic sign. There is a decidedly greater incidence of thickening and contraction of the palmar fascia in alcoholics with hepatic cirrhosis, the basis of which has still not been satisfactorily explained.[320] A chronic, asymptomatic, and noninflammatory enlargement of the parotid glands is observed in alcoholic patients with hepatic cirrhosis.[320b, c] (It has been also encountered in malnutrition due to other causes.)

The finding of *liver enlargement* four or more fingerbreadths below the

GROUP III

Hepatic Disease and Jaundice

direct reacting bilirubin found in the urine, serum, and fresh bile primarily consists of this pigment which has been coupled with two molecules of glucuronic acid to form an extremely water soluble compound [319] Therefore, what was previously referred to as "combined" bilirubin turns out to be free bilirubin and vice versa

With the aid of these aforementioned tests, derangements in the function of the parenchymal cells, the biliary collecting network, and the reticuloendothelial system are often readily defined For example, one might become alerted to the possibility of an intrahepatic malignancy in an anicteric patient when an obscure process in the right upper abdomen or the lower right thorax is present This may be suggested by the finding of partial biliary tract obstruction (an elevated serum alkaline phosphatase level and marked BSP retention) in the presence of a normal serum bilirubin level and normal parenchymal function studies [324] This same selective interference in the excretion of alkaline phosphatase and BSP (but not bilirubin) by the liver parenchymal cells can lead the clinician to the diagnosis of biliary tract infection and partial obstruction when chills, fever, abdominal pain nausea, and vomiting are not accompanied by clinical or chemical jaundice

Chronic infiltrative diseases of the liver, including sarcoid, tuberculosis, Hodgkin's disease, and systemic lupus erythematosus have also exhibited this combination of a low serum bilirubin (below 2 mg per cent) and a serum alkaline phosphatase activity greater than 15 Bodansky units [3, 40] Another instance in which there may be extreme degrees of bromsulphalein retention (along with elevations of the alkaline phosphatase and cholesterol) but normal serum bilirubins may be found in primary or secondary amyloidosis [193] The hypoalbuminemia in these patients is probably more a result of the massive albuminuria than the hepatic dysfunction

When significant hepatomegaly is present the finding of relatively preserved liver function should direct one's attention to such considerations as hemochromatosis and tumor. This is a particularly important concept as it relates to the alcoholic patient with ascites, since an erroneous diagnosis of cirrhosis might be averted if this admonition is kept in mind

Before committing himself to the diagnosis of lupoid hepatitis, the clinician must be aware of the fact that patients with classic cirrhosis or viral hepatitis often experience symptoms referable to the skin and joints and that liver disease *per se* might be responsible for false-positive L E cell tests [9, 7]

JAUNDICE

The numerous causes of retention, obstructive and hepatocellular jaundice are generally well known and will not be formally enumerated here Most of these cases ultimately prove to be due to hepatitis, cirrhosis gallstones, or cancer in the liver, pancreas, or biliary tree When attempting to solve the etiology of jaundice in any given patient, there are no substitutes for the painstaking history the meticulous physical examination, and considered clinical judgment The differential diagnosis of jaundice cannot be made by an I B M machine This issue is clearly pointed out

costal margin in the presence of jaundice is more consistent with tumor, cirrhosis, fatty infiltration, amyloidosis, and hemochromatosis than with viral hepatitis or extrahepatic biliary obstruction[321] Significant hepatomegaly may be present, however, in obstructive jaundice due to a bile duct or pancreatic neoplasm (*vide infra*) The small size of the cirrhotic liver which has served as a substrate for the development of a multicentric hepatoma ("carcinomatous cirrhosis") contrasts with the relative rarity of a very small liver that is the site of metastatic carcinoma[995b] On occasion, tumors, cysts, and anomalies of the stomach colon, and right kidney have been mistaken for hepatomegaly The perfection of the technique for percussing the upper border of liver dullness will frequently help to solve the recurrent problem of an enlarged liver versus a low-lying organ Similarly, the auscultation of a bruit or a friction rub may aid in defining an obscure process affecting this organ

The prognosis in subacute and chronic inflammatory or nutritional hepatocellular disease is much better when the liver is large than when it is not palpable, since hepatomegaly usually also indicates the ability of the organ to regenerate itself For example, a relatively high incidence of hepatomegaly is encountered among elderly patients who are suffering from malnutrition, as indicated by the reversion of the liver to a normal size within three months after an adequate diet is instated[1300]

Another useful clue in the diagnosis of hepatocellular and obstructive jaundice is the presence of *splenomegaly* This is a most important diagnostic guide in infectious hepatitis and in toxic intrahepatic obstructive jaundice with cholestasis when a palpable or tender liver is absent Under these circumstances, an enlarged spleen is relatively uncommon unless a portal or splenic vein thrombosis coexists[322]

Liver Function Tests

Concerning the subject of liver function tests the serum bilirubin, serum proteins, alkaline phosphatase cephalin flocculation, thymol turbidity, 24-hour urine urobilinogen excretion vitamin K response, the sulfabromophthalein (bromsulphalein or BSP) test (in the absence of significant icterus) and more recently the serum transaminase determination should give as much information as is usually necessary, *if* properly performed When a diagnostic impasse has been reached, the liver biopsy technique has proved to be eminently helpful and relatively safe in arriving at a definitive diagnosis and prognosis[323] An analysis of liver function studies can be found in Section IV of Part II

More recent studies dealing with the chemical nature of the bilirubin pigments with respect to their van den Bergh reaction have conclusively demonstrated the following two important facts (1) the nature of their binding to protein has no bearing whatever on this reaction, and (2) the reaction apparently depends on the presence or absence of conjugation of the bilirubin with glucuronic acid in a manner just opposite to that implied by the older terminology Indirect acting bilirubin represents 'free' unconjugated bilirubin, and because of its insolubility in water requires the addition of alcohol to initiate diazo coupling On the other hand the

of urinary urobilinogen On the other hand, the presence of infection above a biliary tree obstruction may result in the presence of urinary urobilinogen

It is very unusual, however, for certain "pathognomonic" signs to be misleading These include the enlarged gallbladder in extrahepatic obstruction, and the association of typical spider angiomata, ascites, edema, and an extensive collateral circulation in patients with prolonged hepatocellular disease

Coexisting Phenomena

The clinician is also reminded of the confusion that is not infrequently encountered when several coexisting phenomena accompany a given case of jaundice These are enumerated in the following list

1 The presence of *gastrointestinal bleeding in an alcoholic* with an enlarged liver is *not* necessarily diagnostic of esophageal varices A *bleeding peptic ulcer* is often encountered under these circumstances[3,5]

2 When obstructive jaundice persists at an intense level and an exploratory operation fails to reveal the site of obstruction, *a carcinoma arising in one of the major hepatic ducts or close to their junction* must be considered The finding of a collapsed gallbladder and common bile duct in this situation should alert the surgeon to this possibility The use of Cholegrafin has been diagnostic in such instances Malignant tumors of the major intrahepatic and extrahepatic bile ducts (exclusive of the papilla of Vater) are practically always adenocarcinomas These lesions have a tendency to spread early by both local and distant metastases and to result in a rapidly fatal course frequently that of hepatic failure with coma[3,6a]

3 Although *diverticula of the second portion of the duodenum pancreatitis,* and *postbulbar ulcers* may produce obstructive phenomena, these are *quite uncommon* causes of jaundice Other causes must be sought out most notably the *cholangiolitic type of hepatitis* resulting from treatment with chlorpromazine, methyltestosterone or a host of other drugs (PAS, sulfadiazine, thiouracil)

4 Should the surgeon happen to find a concomitantly abnormal gall bladder a small *carcinoma at the ampulla of Vater* can be easily missed This may occur even when the common duct has been probed particularly if the duodenum is not actually inspected The presence of persistent jaundice and occult blood in the stools—along with the newer intravenous cholangiographic techniques—can alert the clinician to this diagnosis Even here there are exceptions to the rule since the obstructive jaundice might fluctuate in degree because of the ulceration and sloughing of the tumor[3,7]

5 The alert radiologist can become suspicious of a primary peripapillary malignant *tumor of the duodenum* resulting in obstructive jaundice, even in the absence of bleeding or gastrointestinal obstruction[3,5a] These tumors are not infrequently labeled as carcinoma of the ampulla of Vater

6 Jaundice in the presence of chronic passive congestion of the liver is often due to *pulmonary splenic or renal infarction*[3,6b] (One must remember that the presence of cyanosis or edema may mask the appearance of the jaundice)

on those occasions when two or more diseases are present, wherein even a liver biopsy might not help

The serum transaminase (p 694) and serum iron levels (p 687) have both increased the clinician's diagnostic armamentarium in those instances when the nature of jaundice cannot be readily ascertained Elevations in both occur with hepatic necrosis, but not in the presence of obstructive jaundice * (Approximately 15 per cent of the total body iron exists in the liver)

It is emphasized that the patient with intense jaundice of the obstructive type is rarely injured by a period of one to two weeks of careful observation In fact, the author knows of several patients with severe obstructive-type jaundice who were wisely followed for several months because a drug induced hepatitis was correctly suspected It is also known that hepatocellular function can remain normal for several months in infants born with atresia of the bile ducts[318] The clinician is cautioned concerning the repeated performance of needle liver biopsies in the presence of a mechanical biliary obstruction that is not relieved Under these circumstances, a bile peritonitis or a biliary fistula may result from this diagnostic effort

Since an enlarged gallbladder might be seen in some instances when it cannot be felt, it is wise to look at the abdomen tangentially in a good light, especially with the protrusion of the abdomen during expiration Schiff has pointed out that in the search for a painlessly distended gallbladder in the undiagnosed jaundiced patient, little attention has been paid to the importance of the *absence* of a palpable liver in *excluding* obstructive jaundice due to a pancreatic tumor[3 10] When there is complete and persistent obstructive jaundice the liver becomes engorged with bile and is therefore usually palpable Added support to Schiff s observations comes from the finding of enlarged livers (weighing over 2000 gm) in over one half of the 54 patients who were studied at the Mayo Clinic for carcinoma of the major intrahepatic and extrahepatic bile ducts (exclusive of neoplasms involving the papilla of Vater)[3 64]

Misleading Associations

There are several important *"red herrings" in the approach to the jaundiced patient* which might well be recounted at this point

1 The natural course of cirrhosis or hepatitis (particularly in epidemics) is at times punctuated by acute exacerbations and right upper quadrant pain that may closely simulate other causes of obstructive jaundice

2 A history of alcoholism can be obtained in 15 per cent of patients with obstructive jaundice due to either stones or malignancy

3 Methionine or brewer s yeast administration should be suspected if "fetor hepaticus" is present in an alert patient

4 Pruritus associated with obstructive jaundice does not *per se* indicate whether the basic process is intrahepatic or extrahepatic

5 The administration of antibiotics can significantly reduce the titer

* See reference 57 of Part II

develop when the diagnosis of "chronic hepatitis" is made In view of the newer concepts of direct and indirect bilirubin with respect to the absence of conjugation of the latter with glucuronic acid by the liver,[319] it is possible that the icterus in familial nonhemolytic jaundice may prove to be the result of defects in the enzyme systems that are necessary for such coupling

Chronic Idiopathic Jaundice

For much the same reasons, it is also important to bear in mind the entity of *chronic idiopathic jaundice with unidentified pigment in liver cells* to which attention has been recently directed by Dubin and Johnson [334] Many of these patients experience recurrent attacks of jaundice, often exacerbated either by infections or by operative procedures In the interim, however, they are apparently well It has been suggested that the greater increase of direct bilirubin in this condition (up to 6 mg per 100 ml)—in contrast to the greater increase of indirect bilirubin in constitutional hyperbilirubinemia—may serve as an aid in the differentiation of these two entities Since cellular infiltration is not characteristic of this syndrome, the pigment must not be mistaken for bile stasis in liver biopsy specimens This error could result in the patient being subsequently subjected to a needless exploration for presumed obstructive jaundice

VIRAL HEPATITIS AND ITS VARIANT SYNDROMES

In an analysis of sporadic cases of acute anicteric viral hepatitis, the most frequently encountered symptoms are fatigue, anorexia, distaste for smoking abdominal pains mild joint aches, headache and nausea [335a] The liver may be neither palpable nor tender in a significant number of these patients This diagnostic consideration is equally true in the case of anicteric children with this disease where such nonspecific symptoms as loose stools, fever, failure to gain weight, lassitude, and vomiting often dominate the clinical picture [336a] It has been noted that there is a tendency, even among experienced pathologists to overdiagnose extrahepatic obstruction in infantile liver disorders, and to interpret viral hepatitis and posthepatitic cirrhosis as obscure variants of biliary atresia [336b]

Homologous serum hepatitis can be acquired not only from nonsterile needles and the injection of blood or several of its products, but also from dental work and other procedures which occurred as long as four to six months prior to the actual jaundice [338a] Even when the dental instruments are sterile the trauma may activate the virus of infectious hepatitis which happens to be present as a commensal in the mouth It has been suggested that the viruses producing infectious hepatitis and homologous serum jaundice are actually the same, notwithstanding the differences in their incubation periods and clinical course The prolonged incubation period may be explained by the fact that there is an attenuation of the infectiousness and virulence of the virus particles for one to two months because of their temporary coating with specific antibodies in the blood of the unrecognized carrier [338b] (On the basis of the existing evidence, how

7 Cholelithiasis frequently complicates the hereditary types of *(hemolytic) anemia*

8 An interesting *triad of hyperlipemia, hemolytic anemia,* and *hyperbilirubinemia* has been noted in patients with excessive and persistent ethanolism [326c] In these cases, the liver biopsy reveals either fatty infiltration or a mild portal cirrhosis rather than evidence of obstructive jaundice for which this disorder might be mistaken Rapid improvement of all these abnormalities is forthcoming after the drinking is stopped

9 Chills and jaundice following a bout of lower abdominal pain, with or without ileus, should lead one to suspect a *pylephlebitis complicating appendicitis* [1293]

10 The association of an obstructive type of jaundice with recent, rapid, and unexplained weight loss and no significant anemia is highly suggestive of *pancreatic carcinoma* [1041 1043] It is wise to remember that whereas 75 per cent of gallstone cases occur in women, three out of four patients with this disease are males

11 Obstructive jaundice occurring one or several years after a pancreatoduodenal resection for a carcinoma of the ampulla of Vater may be due to a *benign stricture of the common duct* rather than to recurrence of the previous malignancy [3 8b]

12 When the "postcholecystectomy syndrome" occurs following a properly indicated operation and no residual stones stricture, or pancreatitis can be demonstrated, it is well to bear in mind the entity of *the cystic duct remnant* (Morton's syndrome) [329]

13 Painless obstructive jaundice occurring years after biliary tract surgery has been caused on rare occasions by *amputation neuromas* and by *granulomatous reactions* to the sutures [330]

14 The occurrence of pruritus marked hepatomegaly, and chronic jaundice in the presence of a relatively good nutritional status and without significant anemia should suggest a "*primary*" *type of biliary cirrhosis*

15 Striking instances of abdominal pain jaundice, and marked elevations of the *serum alkaline phosphatase levels* have been *reported* due to *infectious mononucleosis* even preceding the onset of the pharyngitis and lymph node enlargement [331]

16 In the patient who develops jaundice several days following surgery, it is well to be cognizant of the possibility that the combination of (a) the increased hemolysis attendant upon many transfusions, and (b) the impairment of liver function from surgical trauma, transient shock, and anesthesia may be responsible It has been shown that 18 gm of hemoglobin are released and 720 mg of bilirubin produced within twenty four hours after an individual receives 500 ml of blood [33] (The liver normally processes only between 7 and 12 5 gm of hemoglobin daily)

Constitutional Hyperbilirubinemia

One should attempt to recognize promptly the syndrome of *constitutional nonspherocytic hyperbilirubinemia* with its consistently excellent prognosis and benign characteristics [332] This is necessary in order to avoid the frequent psychoneurosis or iatrogenic illness these patients are prone to

Patients with severe hepatitis especially postmenopausal females, may hemorrhage from many sites particularly the gastrointestinal tract and the kidneys This occasionally results in the diagnosis being made of a neoplasm in these organs Such marked hyperestrinism can occur in cases of unrecognized advanced hepatitis or cirrhosis that the diagnosis of carcinoma of the endometrium or a granulosa cell tumor of the ovary may be seriously considered, even supported on occasion by a false-positive vaginal smear test [115] Since the liver tenaciously retains its ability to inactivate estrogen—even at times outlasting its capacity to synthesize urea—the prognosis in this situation is obviously very poor

Another interesting variant of chronic liver disease is to be found in certain young women who exhibit unusual features not commonly encountered in either classic posthepatitic cirrhosis or Laennec's cirrhosis These include the insidious onset of obscure febrile episodes, joint pains and arthritis (particularly of the ankles and wrists), and delayed menstruation or amenorrhea The well nourished and relatively healthy appearance of these patients has been frequently misleading both diagnostically and prognostically Bearn, Kunkel and Slater have reported on a group of 26 such patients (of whom only three were males) They postulate that the usual course of infectious hepatitis is modified in these young women by specific endocrine influences [342]

There is yet another variation of severe hepatic disease in females that may simulate fulminant epidemic hepatitis clinically, but is quite different pathologically This consists of a diffuse fatty metamorphosis of the liver which appears late during the last trimester of pregnancy and is manifested by the clinical and laboratory features of acute liver failure The lobular structure is preserved necrosis in the paracentral zone is absent or minimal, and cellular infiltration may be sparse or absent Severe vomiting epigastric pain hematemesis, intense jaundice and marked neurologic and psychiatric symptoms occur but the usual form of toxemia of pregnancy *per se* is not characteristic It is felt that the pathogenesis of this distinctive but little appreciated syndrome is related to the toxic effect of some endogenous humoral agent or metabolic derangement stemming from the pregnancy itself [343]

Hepatitis, particularly of the homologous serum type, occasionally complicates diabetes mellitus Although no characteristic pattern in the behavior of the diabetes is encountered the general experience has been that the hepatitis is much more prolonged and severe [344]

Intrahepatic Cholestasis

A few additional remarks are in order concerning the increasingly important subject of intrahepatic cholestasis (or "cholangiolitis") (A brief review of the many designations for the various arborizations that constitute the intrahepatic biliary network is in order for purposes of orientation The *bile capillaries* or *canaliculi* are the tiny conduits that are the first to collect the bile from the liver cells They then merge into somewhat larger tubes known as the *cholangioles* or *ductules* These channels

ever, most authorities are disinclined to accept this unitarian concept of a single strain of the hepatitis virus)

Ardmore Disease

Attention has recently been called to Ardmore disease, another acute infection in which there is a markedly tender and enlarged liver[337] It has undoubtedly been mistaken for anicteric infectious hepatitis and infectious mononucleosis in the past The responsible agent is presumably a virus Clinically, the disorder is characterized by considerable pain in the upper abdomen aggravated by any jarring motion an upper respiratory infection, a low grade fever a tender lymphadenopathy (especially involving the posterior cervical nodes), splenomegaly and a tendency to a chronic course with many relapses Two features that are surprising in light of the liver enlargement relate to the rather mild changes observed both in liver biopsy specimens and the liver function tests For example in one series of 63 such patients, significant sulfobromophthalein retention (i e greater than 5 per cent at forty five minutes) could be demonstrated in only 39 individuals Other important negative features include the absence of jaundice the absence of atypical lymphocytes, and the consistently negative heterophile agglutination studies

A number of other infectious diseases can occasionally closely simulate viral hepatitis, among which are infectious mononucleosis,[731] mumps[69] yellow fever, herpes zoster[339b] amebiasis,[617] and Q fever Q fever may produce focal hepatocellular damage splenomegaly or fever of undetermined origin even in the absence of significant pulmonary involvement[339a] On the other hand the predominance of neurologic signs and symptoms in the preicteric phase of infectious hepatitis might suggest encephalitis meningitis, poliomyelitis porphyria or infectious mononucleosis[340]

The decision as to whether significant liver disease is present or not has become quite important when evaluating bizarre functional complaints in the already sizable group of veterans who have had a "hepatitis experience" In an exhaustive study of the prevalence and nature of hepatic disturbance following acute viral hepatitis by the Veterans Administration and the National Research Council Neefe and his committee arrived at the following pertinent conclusions

1 The prevalence of demonstrable severe or active chronic liver disease is *not* significantly higher in those with a previous history of hepatitis and jaundice than in those with no previous history of recognized hepatitis

2 Laboratory evidence of mild hepatic dysfunction may be found in 5 per cent of young adults who have had no recognized hepatitis or unusula exposure to the hepatitis virus

3 Needle biopsy specimens have repeatedly shown the fallacy of drawing conclusions concerning the nature of the hepatic disturbance on the basis of either prior history or current clinical and laboratory data alone

4 The occurrence of symptoms more than three symptom free years following the initial attack of hepatitis should make one consider the probability of a new infection or process rather than an exacerbation of the original disease[341]

of new cholangioles and hepatitis in the precirrhotic phase It may be accompanied by a similar process in the pancreas, both of which can stem from bacterial infection

3 *Pericholangiolitic biliary cirrhosis* results from a low grade, chronic, proliferative pericholangiolitic hepatitis in which the cellular exudate that is so conspicuous in cholangitic biliary cirrhosis is minimal In contrast to secondary biliary cirrhosis due to obstruction or infection (or both) in the major extrahepatic ducts, only the intrahepatic microscopic bile ducts are affected in primary biliary cirrhosis leaving the extrahepatic biliary system intact Furthermore, the hypercholesterolemia, the xanthomatosis, and the large spleen that are found here are unusual in either cholestatic cirrhosis or cholangitic biliary cirrhosis

4 *Acholangic biliary cirrhosis* occurs in children up to twelve years old, with bile stasis, preservation of the lobule and perilobular fibrosis resulting from some congenital defect involving the interlobular bile duct system

5 *Fibroxanthomatous biliary cirrhosis* is the least common type It is a component of generalized xanthomatosis and is characterized by the infiltration and proliferation of cholesterol laden histiocytes in the portal areas[345a, b]

The situation may be further complicated by the simultaneous presence of two or more types (most notably cholestatic cirrhosis and cholangitic biliary cirrhosis) or by a superimposed infection affecting the terminal bile ducts It is more than likely that many of the cases previously diagnosed as Hanot's cirrhosis were variants of chronic hepatitis

Since the diagnosis of the ' nonsurgical *primary pericholangiolitic biliary cirrhosis* is unfortunately usually established at laparotomy, it is well to review briefly the features of this disease Classically, it occurs in middle-aged women who are chronically jaundiced, pruritic and melanotic, but usually appearing rather robust and active The onset is often insidious, with the pruritus preceding the advent of the icterus by weeks or even months Although the liver is enlarged (at times to an enormous size), abdominal pain or colic fat intolerance, chills and fever are conspicuous by their absence Hyperlipemia xanthomatosis, clubbing of the fingers, steatorrhea, or osteomalacia may ensue Ultimately, after many months or years of spontaneous remissions and exacerbations, the signs and symptoms of hepatic insufficiency and portal hypertension supervene[347]

Inasmuch as the liver function studies characteristically point to biliary obstruction the atypical cases of this condition may prove to be a diagnostic enigma For example, the patient is at times a male who exhibits considerable weight loss, fat intolerance abdominal pain, and a febrile course Movitt has reviewed his experiences with the liver biopsy technique in this disease[348] He feels that the following three features can help in distinguishing primary biliary cirrhosis from extrahepatic biliary obstruction

1 the virtual disappearance of bile ducts from the portal spaces in the primary disease in striking contrast to the preservation or reduplication of these structures in both secondary biliary cirrhosis and Laennec s portal cirrhosis,

spread from their *intralobar* origins into the *perilobular* areas, from whence they merge into the *interlobular bile ducts*.)

A number of clinicians and pathologists have shown that this condition actually represents a nonspecific response and that it may be either a component or complicating feature of hepatitis and cirrhosis. It is also the occasional predominant feature of drug hypersensitivity or of some as yet undetermined etiology. While *it can on occasion proceed to biliary cirrhosis*—with or without dermal xanthomas—severe liver cell degeneration does not generally occur.[3,2] The author has found the presence of significant quantities of urinary urobilinogen to be very helpful in evaluating the patients with chlorpromazine hepatitis whom he has encountered.

It is stressed that there is no characteristic lesion found on liver biopsy (a procedure which obviously cannot give the total picture of intrahepatic or extrahepatic biliary obstruction throughout the liver). Even the most capable pathologists have found it virtually impossible to differentiate between extrahepatic obstruction and chlorpromazine hepatitis in liver biopsies.[3,26] The problem is further confused by the fact that initial functional derangements of the biochemical and physiological processes in the biliary system may be subsequently furthered by both the pericholangiolar inflammation and the mechanical bile stasis.

In one series of 22 cases of chlorpromazine jaundice a mild to moderate eosinophilia was encountered in over 80 per cent of the patients, which the reporting clinicians regarded as suggestive evidence that this is an allergic state.[3,4] Another indication of the probable allergic basis for chlorpromazine jaundice stems from the reappearance of icterus on subsequent challenge doses of this drug, even as long as seventeen months following the initial hepatitis.[1164b] The use of intravenous ACTH in this type of diagnostic dilemma might prove to be a valuable therapeutic test if a prompt and striking clinical-biochemical response ensues.[32-b] (The occasional drop in serum bilirubin that has been observed in patients with proved extrahepatic obstructive jaundice must be borne in mind also.)

It is again apparent, however, that when faced with such a situation of "medical" versus "surgical" jaundice, the clinician must often resort to the considered clinical judgment and "intuition" that comes with experience. If the various parenchymal tests of liver function are relatively preserved after an adequate period of observation, surgical exploration may prove to be the wisest course of action. It is necessary to remember that the onset of jaundice due to chlorpromazine and other drugs may occur two weeks or longer after the last pill or injection was taken.[3,c]

BILIARY CIRRHOSIS

MacMahon has authoritatively analyzed the five histological types of so-called biliary cirrhosis.[346] They will be briefly reviewed here for purposes of orientation to this complicated subject.

1. *Obstructive or cholestatic cirrhosis* (the commonest type) is induced by prolonged obstruction of a major hepatic or biliary duct, and is characterized by centrolobular bile stasis.
2. *Cholangitic biliary cirrhosis* exhibits an inflammatory proliferation

Hepatic Coma

The presence of blood in the gastrointestinal tract *per se* may exert a deleterious effect in the patient with cirrhosis and can induce 'hepatic' coma. Whereas the introduction of whole blood into the intestines of both man and dogs is followed by a relatively innocuous azotemia that is predominantly due to a rise in the blood urea, the cirrhotic individual (who already has natural portacaval shunts) will experience marked elevations in the blood ammonia.[35b] Consequently, endogenous ammonia formation in the colon may be checked in these cases not only by the antibiotics, but by purging and enemas.

This is far from an academic consideration in view of the repeated demonstration that both the neurologic manifestations and the elevated blood ammonium levels in "endogenous" hepatic coma can be promptly reversed in some instances by altering the intestinal bacterial flora with certain antibiotics, as neomycin,[153] or with sodium glutamate therapy. (One of the chief mechanisms by which ammonia toxicity occurs is explainable by the disturbance that takes place in the Krebs cycle, wherein one of the metabolites, alpha ketoglutaric acid, is depleted. This results in a diminution of oxidative phosphorylation and oxygen utilization. The reason for the use of large doses of glutamate therefore is the fact that ammonia becomes fixed with alpha ketoglutaric acid, in turn forming glutamic acid which then combines with a second ammonium ion to produce glutamine.)

Several additional comments are in order concerning hepatic coma. While this condition may actually be quite difficult to distinguish from a number of other entities, most notably uremia, such a differentiation is important in planning therapy. For example, it is vitally important that Wernicke's encephalopathy not be misdiagnosed as hepatic coma due to the salutory effects of large doses of thiamine in the former state.[142, 355] The importance of not overlooking hepatic hypoglycemia (p. 21) and magnesium deficiency (p. 67) as causes of bizarre mental behavior, neurologic phenomena, and coma have been discussed previously.[61, 41] Although the so-called "flapping tremor" was at one time thought to be characteristic of hepatic failure, it has also been observed in pulmonary insufficiency,[1112] renal failure, polycythemia vera, severe malnutrition and steatorrhea.[356] Two other important and potentially treatable conditions that must be considered in the alcoholic patient with cirrhosis who develops serious neurologic involvement are a subdural hematoma and an infectious meningitis.[142d]

In view of the dynamic relationship between the synthesis and excretion of urea, a low blood urea nitrogen is not necessarily a constant feature of severe liver damage. The issue is further complicated by the fact that renal failure does occasionally accompany hepatic failure (the "hepatorenal syndrome"), especially when variceal hemorrhages introduce the factor of "prerenal" azotemia. Inasmuch as an elevated blood ammonia concentration is invariably absent in uremia, this determination suggests itself as a worthwhile basis for differentiating these states if it is available.

2 the periportal instead of pericentral distribution of the bile thrombi, and
3 the presence of bile "lakes," bile infarcts, and bile extravasates in the portal tracts, which tend to rule out primary biliary cirrhosis as well as the other types of intrahepatic obstructive jaundice

PORTAL CIRRHOSIS AND ITS COMPLICATIONS

Attempts are continually being made to define and classify *cirrhosis* along morphologic, etiologic, and functional grounds, and to do away with such confusing terms as perilobular cirrhosis, hypertrophic cirrhosis, atrophic cirrhosis, and capsular cirrhosis There is not necessarily any correlation between the degree of hepatic fibrosis found on biopsy and the clinical signs or symptoms of hepatic failure Profound improvement may ensue in many of these patients when they are placed on an adequate dietary and therapeutic regimen, due to the regression of the parenchymatous changes [349] It is of interest that a significant number of livers examined post mortem following hepatic failure show changes that are intermediate between those of the classical Laennec's cirrhosis and postnecrotic cirrhosis

When the patient with Laennec's cirrhosis exhibits fever and a progressive downhill course fairly rapidly, the possibilities of a complicating *hepatoma* an *infected ascites*, a *portal vein thrombosis*, and *tuberculosis* should be entertained The presence of significant leukopenia, thrombocytopenia, anemia, or varying combinations thereof in the cirrhotic patient may be indicative of a true *hypersplenic effect* Crampy abdominal pain ("pseudogallstone colic") can occur in patients with cirrhosis or hepatitis, for which surgery might even be contemplated [1186c]

COMPLICATIONS OF THERAPY

A review of the patient's therapy is also in order when unexplained morbidity occurs in cirrhosis Oral *methionine* may precipitate neurologic deterioration in patients with liver disease, without necessarily elevating the peripheral venous ammonia levels [350] Large doses of *niacin* can prove detrimental by inducing marked fatty infiltration of the liver (Since this vitamin has to be methylated in the liver, it may compete for the methyl groups of methionine and choline)[351] Anorexia nausea vomiting and profound weakness may be due to a *low salt syndrome* following vigorous therapy for the edema and ascites [303]

One must also be sure that the factor of *ammonium intoxication* has not been inadvertently introduced through the forcing of high protein diets or protein hydrolysates, and by the administration of chlorothiazide, Diamox, urea, ammonium chloride, or ammonium resins as diuretics in the presence of severe liver disease [352] It is felt that the inability of cirrhotics to clear ammonia from the blood is partially related to the formation of vascular shunts which bypass the liver Such a concept is supported by the observations following liver shunting operations[354] and the rare formation of a spontaneous Eck fistula in man [354b]

hepatic necrosis which could not be explained on the basis of eclampsia, associated shock or cardiac failure, necrosis associated with abscess formation, intrahepatic neoplasms or cirrhosis, "subacute yellow atrophy," gram negative bacteremia, chemical poisoning, and the ischemic liver necrosis associated with polyarteritis and other vascular diseases[358a] Furthermore, after those instances that were associated with direct trauma and hepatic vascular occlusion were excluded, no anatomic mechanism for the necrosis could be ascertained in the remaining 82 per cent It is possible that the administration of the vasopressor amines might accentuate these lesions as can be produced experimentally *Infarction of the liver* on the basis of an embolic or thrombotic occlusion of the hepatic artery system or the portal vein *per se* is not common having been found only 37 times in 18,340 consecutive autopsies performed at the Mayo Clinic[358b]

Ascites of Obscure Origin

A considerable degree of accuracy can be achieved in diagnosing ascites of obscure origin by supplementing the usual diagnostic procedures with a careful gross microscopic bacteriologic chemical, histologic and cytologic study of the ascitic fluid[359] In the case of *transudates*, one must consider (1) hypoproteinemia (hypoalbuminemia the nephrotic syndrome), (2) liver disease producing portal obstruction (cirrhosis, hemochromatosis, hepar lobatum), (3) extrahepatic obstruction of the portal vein (*vide infra*) (4) the Budd Chiari syndrome and (5) increased pressure above the hepatic vein (inferior vena caval obstruction, congestive heart failure tricuspid stenosis, constrictive pericarditis, and mediastinal tumors or inflammation)[360]

In dealing with obscure ascitic *exudates*, the diagnostician must entertain the diagnoses of infectious peritonitis (particularly tuberculosis and peritonitis complicating disease or rupture of the abdominal viscera), peritoneal malignancy (carcinomatosis from the stomach, bowel pancreas or ovary, and lymphoma), polyserositis (p 313), the Meigs-Cass syndrome (p 35), pseudomyxoma peritonei (p 345), and peritoneal mesothelioma (p 346) Reference to most of these etiologies is made throughout the text Unusual types of ascitic accumulations can result from the presence of blood, lymph, or bile

The Budd-Chiari Syndrome

Another less frequent disorder that may either complicate liver disease or simulate portal thrombosis cirrhosis, constrictive pericarditis and inferior caval obstruction is the Budd Chiari syndrome It might result from an intrinsic endophlebitis involving the hepatic veins or their ostia, or from an obstruction of the inferior vena cava at the level of the caval fossa The etiology and clinical picture have been ably summarized by Palmer[361] Malignant obstruction (hepatoma, intraluminal extension of malignant tumors along the inferior vena cava) polycythemia vera[633] sickle cell disease constrictive pericarditis, leukemia, diffuse or localized liver disease, and thrombophlebitis of the inferior vena cava are most

Endocrine Induced Changes

Profound endocrine-induced changes may occur in hepatic insufficiency, presumably due to the inability of the damaged liver to inactivate or excrete endogenous estrogens as rapidly as normal These include severe testicular (tubular) atrophy and marked hyperplasia of the breasts (the Klinefelter syndrome), decreased libido and potency, decreased body and axillary hair, menstrual irregularities, and the previously cited telangiectasia and "liver palms"[357] Occasionally, doubt arises as to whether one is actually dealing with a Klinefelter syndrome due to primary hypogonadism in an alcoholic[357c] In such an instance, there is hypergonadotropism, this is in contrast to the low or normal levels of I SH encountered in cirrhotics

The cutaneous manifestations of the Klinefelter syndrome are depicted in Figure 60 (Atlas page 38)

In a pathologic study of 100 patients with cirrhosis, including 17 who also had hepatomas, evidence of excessive estrogenic effects could be found in 85 per cent of the females and in over 90 per cent of the males[357a] The frequency with which pituitary basophilism of the gonadotropic type was encountered in men with concomitant cirrhosis and hepatoma suggested the possibility that the estrogen may have exerted a co-carcinogenic effect in these individuals

Other Sequelae of Vascular Shunts

The presence of oxygen unsaturation of the arterial blood in patients *with cirrhosis of the liver—especially in the absence of any defect of* alveolar capillary diffusion—has suggested that an abnormally large venous admixture may be taking place, probably due to anatomic shunts which by-pass the lungs Anatomic studies have, in fact, demonstrated the existence of both portacaval and portapulmonary anastomoses in patients with cirrhosis and portal hypertension, similar to those found in patients with heart failure[345] It is quite likely that when the pressure gradient between the portal and the pulmonary veins becomes great, these anastomoses (especially in the periesophageal plexus and in the mediastinal venous plexus) may allow the circulation to by pass the lungs A point of further interest in this regard pertains to the fact that the azygos vein may be enlarged not only in heart failure, but also in cirrhosis This presumably reflects the caval venous hypertension, the increased blood volume, the increased azygos flow from the portal venous collaterals, or any combination of these factors[345]

OTHER DISORDERS OF THE LIVER AND HEPATIC CIRCULATION

Unexplained Hepatic Necrosis and Infarction

Pathologists and also many clinicians are currently encountering an increased incidence of *unexplained hepatic necrosis* For example, a careful study of the autopsy and clinical records of 3229 patients admitted to the University of Minnesota Hospitals in recent years revealed 62 cases of

More often, however, the extrapyramidal neurologic symptoms of tremor, dysarthria, ataxia rigidity, and personality change initiate the clinical syndrome

The demonstration of the Kayser Fleischer ring (a unique deposit of greenish brown pigment on the undersurface of the corneal limbus) in such a symptom complex is diagnostic Since this manifestation is found in only half the cases and is often minimal, it may be necessary to resort to the use of the slit lamp to identify it positively Uzman and Jakus have reported on the histochemical and electron microscopic findings in the cornea of patients with hepatolenticular degeneration, with particular reference to the manner in which the copper depositions occur [364c]

A most unusual physical sign in certain cases of Wilson s disease consists of the azure blue discoloration of the lunulae of the nails of the hands [364d]



commonly the basis for such a reaction, resulting in the subsequent congestion and eventual atrophy of the liver

In the *acute form*, there may be severe right upper abdominal pain nausea, vomiting, a rapidly enlarging and tender liver, splenomegaly and ascites Hepatic coma usually ensues within a period of several weeks The severity of the clinical picture depends on the rapidity and degree of the hepatic vein obstruction and the efficiency of the collateral venous channels In the more *chronic form*, a gradual enlargement of the liver and spleen, the development of an ascites that is resistant to diuretics, and an early marked retention of bromsulphalein occur Hydrothorax, jaundice, and edema of the legs also occasionally appear

Chronic Extrahepatic Obstruction of the Portal Vein

It is of clinical and prognostic significance that the majority of cases of portal hypertension due to chronic extrahepatic obstruction of the portal vein do *not* exhibit ascites when a well developed accessory portal venous network (hepatopetal circulation) exists In these instances, the degree of splenomegaly and liver atrophy are usually considerably lessened than when ascites is present [36] The causes of portal vein obstruction are legion and include thrombosis, cavernous transformation infection, tumor invasion, polycythemia vera [682] and other blood dyscrasias A number of unusual causes for portal system hypertension have appeared in case reports, such as compression of the portal vein by recurrent acute pancreatitis,[1353] the pressure exerted by granulomatous lymph nodes infected with *Cryptococcus neoformans* extensive phlebosclerosis of the hepatic and portal veins, and thrombosis of the splenic vein caused by a retroperitoneal inflammatory mass [362b]

Hepatolenticular Degeneration

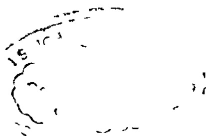
In the presence of unexplained or familial cirrhosis and neurologic manifestations—particularly in patients under thirty years of age—the clinician would do well to think of hepatolenticular degeneration (Wilson's disease) [363] *This is fortunately no longer solely an academic consideration*, since greater understanding of the copper and protein derangements that are characteristic of this state (hypocupremia hypercupruria, hypouricemia, and hyperaminoaciduria) makes rational therapy with the copper chelating agents possible [364] Inasmuch as marked hypouricemia is encountered only in Wilson s disease and the de Toni Fanconi syndrome, the very simple determination of the blood uric acid may be of value when the former disorder is being considered [365]

While the liver involvement has been found to precede the brain disease in the few cases studied pathologically, the clinical mode of onset can be quite variable The symptoms of hepatic insufficiency (splenomegaly, ascites, jaundice) may not be apparent even though impaired liver function and the presence of cirrhosis by a liver biopsy are found In 5 per cent of patients with Wilson s disease death due to cirrhosis (the "abdominal form") occurs before any neurologic manifestations are evident [363]

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complicating cardiac surgery Sequelae of healed endocarditis Bacterial endarteritis and secondary endocarditis

PNEUMONIA OR PNEUMONITIS OF OBSCURE ETIOLOGY—DIFFERENTIAL DIAGNOSIS

General considerations Bacteria Systemic mycoses and parasites Viral and rickettsial agents Allergic and collagen diseases The granulomatous disorders Physical agents Cardiac, vascular, and renal disorders Acute interstitial pulmonary fibrosis Neoplasms Nontuberculous pulmonary cavities and pseudocavities

MENINGITIS AND MENINGISMUS OF OBSCURE ETIOLOGY—DIFFERENTIAL DIAGNOSIS

Subdural abscess or empyema Thrombophlebitis of the intracranial venous sinuses Congenital dermal sinus Endocarditis Staphylococcal epidural abscess Brain abscess with bronchiectasis 'Paradoxical' cerebral abscess Meningovascular syphilis Poliomyelitis Epidemic neuromyasthenia Tick paralysis "Benign aseptic meningitis Tuberculosis Scarlet fever Polyneuropathy Neurologic meningeal crises in systemic diseases Torulosis Viral encephalitis Rabies Meningeal neoplasms Iatrogenic meningitis

COMPLICATIONS OF ANTIBIOTIC THERAPY

Resistance Alterations of flora Superinfection Interference with antibody formation

Pseudomembranous Enterocolitis and Tracheobronchitis

SYSTEMIC CONDITIONS PREDISPOSING TO REPEATED SEVERE INFECTION

Diabetes mellitus Hypoparathyroidism Amyloidosis Boeck's sarcoid Chronic alcoholism Cirrhosis Nephrosis Steroid therapy Systemic lupus erythematosus The antimitotic drugs The leukemias (monocytic) The lymphomas Myeloma Sickle cell anemia The disseminated reticuloendothelioses Neutropenia Splenectomy Splenic agenesis

Hypogammaglobulinemia (Agammaglobulinemia)

SOME of the most perplexing diagnostic problems, including many "fevers of unknown origin are ultimately found to be due to one of the illnesses listed in the chapter outline On numerous occasions in these instances, an important part of the complete physical examination—particularly that of the rectum and pelvis—had been originally neglected In other instances, shotgun" antibiotic therapy was instituted prior to sufficient observation and study because "the patient expected to be treated But more often than not prolonged febrile and debilitating illness remains undiagnosed because the underlying disease is not even considered The importance and

GROUP IV

Fever and Infection of Obscure Origin

General Considerations

UNEXPLAINED FEVER

General considerations Physiological variants Factitious fever

NONINFECTIOUS CAUSES OF OBSCURE FEVER

Nervous system disorders Neoplasms Impaired heat dissipation Tropical anhidrotic asthenia Complications of heat exhaustion Anicteric hepatitis Cirrhosis Regional enteritis Ulcerative colitis Heart failure Drug hypersensitivity Localized infarction, necrosis or the accumulation of blood Uterine fibroid degeneration Tick bite fever Periodic fever The granulomata The dyscollagenoses

LOCALIZED AND NONCOMMUNICATING ABSCESSES

Liver Biliary tree Subphrenic spaces Lung Pelvis Bowel (diverticuli, appendix) Sinuses Uterus Psoas area Phlebitis Periodontal infection

URINARY TRACT INFECTIONS

Cortical Abscess

Perinephric Abscess

Pyelonephritis

Necrotizing Renal Papillitis

Significance of bacteriuria

Prostatitis

Seminal Vesiculitis

Acute Hemorrhagic Cystitis Caused by Pleuropneumonia like Organisms

ACUTE AND SUBACUTE BACTERIAL ENDOCARDITIS

Variant presenting syndromes Significance of blood cultures Infected splenic infarct Right sided endocarditis Septic thrombus Infected aneurysm Bacterial and aseptic endocarditis with advanced malignancy Endocarditis

rapid defervescence in the absence of diaphoresis and (5) the recording of a fever of 106 degrees F or higher (which is actually a relatively rare phenomenon in adults) Inasmuch as these individuals can be rather ingenious in the methods they employ to produce spurious hyperthermia—just as they can in the other factitious disorders, such as hypoglycemia, thyrotoxicosis, hematuria purpura and dermatitis—this deception can only be established by (1) having the attendant hold the thermometer in place (2) recording temperatures from several sites without leaving the patient, and (3) taking the temperature of freshly voided urine In fact, one might encounter several of these factitious illnesses in the same patient

NONINFECTIOUS CAUSES OF OBSCURE FEVER

Certain *cancers* are notorious for their ability to mask their identity initially in the form of unexplained fever Retroperitoneal and other lymphomas (p 184), hepatoma (p 96), Ewing s tumor of bone carcinoma of the pancreas (p 328), and carcinoma of the kidney (p 332) are several such frequent masqueraders Pyelography and complete gastrointestinal x rays should therefore be routine procedures in the evaluation of patients with obscure fever [37] In this regard it is pointed out that carcinoma of the ampulla of Vater with partial biliary obstruction has been neglected in the consideration of the causes of obscure fever This disease can produce the characteristic Charcot s fever for as long as two years with but little jaundice [373]

The pyrexia in malignancy may be continuous remittent, relapsing or intermittent It might be prominent even when the tumor is well localized *If fever persists after removal of the primary lesion* however metastases are usually present

Occasionally one encounters a patient with prolonged "*neurogenic fever*" due to increased muscular activity This is most apt to be the case in the myopathies other neurologic states that functionally or organically affect the heat regulatory centers and the tension coincident with great emotional stress (For example the author has had under his observation for some time a middle-aged female with noncyclic body temperatures ranging from 100 to 102 degrees After prolonged and intensive study and therapy by many clinicians nothing more could be conclusively demonstrated than a severe anxiety state with depression) Psychogenic fever or habitual hyperthermia stemming from anxiety provoking situations is probably due to a lability of the thermoregulatory apparatus, which in turn is under the control of the autonomic nervous system and the hypothalamus It must be distinguished from factitious fever [369]

High fever unaccompanied by leukocytosis tachycardia sweating or an increased sedimentation rate has been observed in the *hypothalamic syndromes* Certain barbiturates may relieve this type of fever which is usually not responsive to the antipyretics Hyperthermia may complicate therapy with chlorpromazine and other drugs that act on the brain centers particularly during hot weather This sequel has even suggested heat stroke [1164b]

Insufficient heat dissipation—as may occur in extensive skin disorders,

elusiveness of many serious infections (especially bacterial pneumonia, meningitis, and bacterial endocarditis) is underscored by the fact that this group of diseases represented the most frequent misdiagnoses in a careful study of the diagnostic errors encountered during a recent review of 1106 autopsies at one large center[4b] In an antibiotic era, this poses a very sobering consideration

UNEXPLAINED FEVER

It has been estimated that 40 per cent of patients with a prolonged low grade fever will eventually develop features that permit a diagnosis, 50 per cent will recover without the diagnosis being established, and 10 per cent will continue to be febrile without a definitive diagnosis being made[365, 366] Bottiger finally established the diagnoses in 22 per cent of 158 patients with fevers of unknown origin, these included tuberculosis malignancy rheumatic fever, disseminated lupus erythematosus, non specific infections cirrhosis of the liver, and adrenal disease[367] In 80 cases gathered by Keefer in which the cause of the fever was eventually determined, 51 were due to specific infections, 10 to tumors nine to diseases of the blood forming organs, seven to disorders of the heat regulating mechanism, and three to cirrhosis of the liver[368]

Several comments are in order at this point concerning *the significance of an elevated body temperature* A charting of the frequency curve of the body heat in a large group of presumably healthy individuals will reveal that the upper limit of normal is actually 100 degrees orally[370] Pregnancy ovulation a recent meal or cigarette and menstruation can all induce elevations On the other hand fever may be low grade or even absent in the presence of severe infection, particularly in the aged It will also be pointed out that fever of obscure origin may be associated with interference in the brain's heat regulating center by infection tumor, exogenous and endogenous toxins and vascular accidents

It is not amiss to call attention briefly here to the virtual impossibility of properly sterilizing thermometers in the short time between temperature-taking rounds in most hospitals Since communal thermometers can convey or disseminate infectious hepatitis tuberculosis, diphtheria scarlet fever poliomyelitis, influenza the common cold antibiotic resistant staphylococci and a host of other infections it has been strongly recommended that each patient be supplied with his own thermometer[377]

Sooner or later, clinicians are chagrined after a prolonged and costly search for the cause of a fever to find that they have been duped by deliberate fraud The possibility of *factitious fever* should be seriously entertained under certain circumstances These have been reviewed in detail by Petersdorf and Bennett[369a] They include the following (1) unexplained fever in nurses in patients with hysteria or other overt psychiatric aberrations, and in individuals who are familiar with hospital routines, (2) failure of the temperature curve to correlate with the normal diurnal gradient of body temperature (that is, higher in the late afternoon and early evening) (3) a normal pulse coincident with abrupt spikes in temperature (which has even led to an erroneous diagnosis of typhoid fever), (4) a strikingly

This premise fits in well with the observation that the exposure of normal individuals to high environmental temperatures apparently activates the adrenal cortex to liberate more of the mineralocorticoid aldosterone but invokes very little change in the output of the glucocorticoids[377b] Derangements in this response may contribute significantly to the pathogenesis of heat induced disorders

Several additional entities that can result in obscure fever will now be cited because they are infrequently considered when their classic signs and symptoms are not present *Anicteric hepatitis* and *cirrhosis of the liver* commonly present this problem In the absence of significant diarrhea *regional enteritis*[168] and *ulcerative colitis* have baffled clinicians as causes of unexplained illness and fever (p 49)

Heart failure may be associated with an elevated temperature, even in the absence of infection or pulmonary infarction[369] This is particularly apt to be a problem when valvular disease exists (p 114) or following a myocardial infarction (p 271) In contrast to the weight loss that usually accompanies infectious disease, however there is often a weight gain in occult congestive failure Unexplained fever may follow the application of tourniquets to the limbs of a patient who was in severe heart failure This can be explained in part by the impairment of heat dissipation via the skin on the limbs distal to the site of the induced bloodless phlebotomy[831]

Pyrexia is caused by *hypersensitivity* to various oral and parenteral drugs much more commonly than is suspected There may or may not be an associated eruption The barbiturates, the sulfonamides, penicillin quinidine, the thioureas and iodide preparations are noteworthy in this regard, but the list is legion For example, the author has encountered drug fevers from the use of Aureomycin and isonicotinic acid hydrazide, even though this complication has been reported only infrequently (p 152)[380] [381] A localized inflammatory process at the site of a previous drug or serum injection could alert one to this diagnosis

The sterile inflammation associated with *infarction or necrosis of tissue* anywhere in the body (including that due to radiation injury) and *the accumulation of blood* either in the intestinal tract or within the body cavities may produce obscure fever *Degeneration of a uterine fibroid* is an example of the former[381] Several observers have reported cases of *slowly leaking atherosclerotic abdominal aneurysms* that were manifested by two to three weeks of unexplained fever, leukocytosis few abdominal symptoms and a progressive decrease in the hemoglobin and red blood cell count[38]

Tick bite fever is an important consideration with individuals who are exposed to ticks in endemic areas since removal of the tick will result in a prompt cure[383] *Periodic fever the granulomata* and *the collagen disorders* are discussed in later chapters as causes of prolonged pyrexia

LOCALIZED AND NONCOMMUNICATING ABSCESSES

Localized and noncommunicating abscesses in the liver, the biliary tree the kidneys the subphrenic spaces the perinephric space and the pelvis can be extremely deceptive and should be actively sought in cases of obscure prolonged fevers The same applies to sinusitis, bronchiectasis, chronic mediastinitis, a perirectal or psoas abscess, and an infected abortion

previously sympathectomized patients, and therapy with medication that interferes with normal perspiration—should also be considered in the presence of obscure fever, particularly in the very young or old. Heat hyperpyrexia *may be the result of anhidrosis due to either an intrinsic central failure of the sweating mechanism, or to the peripheral obstructive type in miliaria ("prickly heat")* that is associated with sweat retention (because of the mechanical closure of the sweat pores by keratin plugs) and its sequelae.[1406–1408]

Particular attention should be paid to the entity of *tropical anhidrotic asthenia*, which is often a subtle heat disease related to the incipient loss of acclimatization. (There are a number of other terms which have been used to designate tropical anhidrotic asthenia.) This condition must be suspected when, after a period of apparent good health in tropical weather, the individual complains of asthenic symptoms, exhaustion, headache, dyspnea and giddiness, especially while working in the heat. The papules of the extensive anhidrosis on the covered areas (usually classified as miliaria profunda) manifest a considerable increase in size following vigorous sweating.

This entity must obviously be differentiated from the two other common types of heat disease, namely, "heat stroke" due to a central failure of the heat regulating mechanism, and classic "heat exhaustion" resulting from a salt deficiency dehydration of the extracellular type.[1408] Whereas the heat exhaustion is usually curable by the use of isotonic sodium chloride solution, anhidrotic asthenia is not. It is pointed out that the elevation of the body temperature alone is *not* a reliable guide in differentiating these two disorders. The subject of miliaria is further considered under Group XVII (p. 528).

In this category, the absence of sweat glands in the *ectodermal dysplasias of the anhidrotic type* should also be cited. This is a condition that might be easily overlooked, *especially if it only partially involves the body*.[374] These patients are fairly comfortable in cool environments, but they become very dyspneic and febrile as the warm weather approaches.

Attention is directed to a number of neglected nonelectrolytic complications of *heat stroke and heat exhaustion*. These include decreased prothrombin activity and thrombocytopenia resulting in purpura, hepatitis with midzonal necrosis, and cardiac changes with subendocardial and septal wall hemorrhages.[3, 5, 3, 6] The breakdown of the heat regulating mechanism, characterized by cessation of sweating and subsequent hyperpyrexia, *usually follows a protracted heat spell with excessively high night temperatures*.[377] This chain of events may be unknowingly precipitated or aggravated in preparing patients for various surgical procedures, particularly in areas that are insufficiently cooled and aerated. The use of atropine, the prolonged restriction of fluids and food, and the use of gowns and drapes which reduce the cooling effects of convection and evaporation are at times contributory.[3, 8]

It appears probable that the diencephalon controls the secretion of aldosterone to a larger extent than the pituitary. This is shown by the little effect that hypophysectomy or the administration of those steroids which suppress the release of ACTH exert on the excretion of aldosterone.

and tumors arising in the pelvic organs The lateral film of the abdomen may be of considerable help in suspecting the presence of an infection within the space of Retzius if the ' cleavage planes are not visualized [136]

The reader need hardly be reminded of the many deceiving courses which *appendicitis* often takes, particularly in the elderly in the pregnant woman, and during the course of other acute and chronic diseases (p 488) [386 11 5] Appendicitis that originates from an appendix which lies within the pelvis may be accompanied by very little pain, tenderness, or spasm, notwithstanding the imminence of perforation

While coproliths may bear no clinical significance, their correct identification in a patient with acute abdominal symptoms may be extremely valuable Berg and Berg have stated that in such a situation, there is a 90 per cent chance that the individual has acute appendicitis, and a 48 per cent chance that the appendix is either gangrenous or has perforated [386c] (It is obvious that coproliths must be differentiated from bone islands ureteral and vesical calculi calcified mesenteric lymph nodes phleboliths foreign bodies, and calcification of the appendices epiploicae or ovaries)

Several erious types of *phlebitis* requiring prompt recognition may herald their clinical course by obscure fever and chills These include pylephlebitis (p 466), lateral and cavernous sinus infection and thrombosis (p 134), pelvic thrombophlebitis, and the suppurative phlebitis encountered in drug addicts The subject of obscure thrombophlebitis and its diagnostic import is further discussed under Group VIII (p 214)

URINARY TRACT INFECTIONS

Cortical Abscess

The possibility of renal tract infection merits particular emphasis in the presence of obscure fever A cortical abscess of the kidney due to a metastatic staphylococcal infection from a primary focus elsewhere may be associated with normal studies (urine white blood count and pyelography) Only following extension of the infection to the perinephric tissues, the renal pelvis or the renal veins several weeks later do localizing features occur

Perinephric Abscess

It is estimated that 25 per cent of the cases of perinephric abscess are not associated with pyuria This condition may persist literally for many months or years without the diagnosis being correctly made [387] It can result from a cortical abscess or from the extension of an infection in some neighboring organ, as an infected carcinoma of the bowel cholecystitis, retroperitoneal appendicitis and spinal tuberculosis

Pyelonephritis

The peculiarities of pyelonephritis as an infectious disease and as a bacteriologic enigma have been ably reviewed by Beeson [388] He emphasizes

Diverticulitis is the probable cause of a number of cases of fever of undetermined origin, by virtue of both the local abscesses and their communication with *small branches of the inferior mesenteric vein*. Even when marked chills occur, the blood cultures are apt to remain negative because of the bacteria being filtered out of the circulation by the liver.

The temptation to incriminate tonsillitis, cholecystitis, periodontal disease, and chronic appendicitis as hidden "foci of infection" in these cases of obscure fevers should be avoided when convincing evidence is lacking. On the other hand, there has been an unfortunate dichotomy between the attitudes of the medical and dental professions to this subject—resulting in large measure from the reaction of the former group against the excesses wrought during the era when the doctrine of "focal infection" prevailed. As a result, many physicians now fail to appreciate the fact that *periodontal infection* can, in fact, give rise to hectic fevers and systemic complaints without there being obvious evidence of local inflammation in the mouth. This is most noteworthy in the case of children with deciduous teeth, the greater vascularity of which not only more readily predisposes to bacteremia, but also explains the occasional paucity of changes (even by x-ray) in the presence of considerable periapical suppuration.[384]

Whereas a single *abscess of the liver* is usually caused by *Entamoeba histolytica*, multiple abscesses are commonly secondary to a cholangitis or another focus of infection in the portal venous system. Unfortunately, suppuration in the liver is often not suspected until the condition is further complicated by a subphrenic abscess, an empyema, a lung abscess, or peritonitis. Nonamebic hepatic abscesses have been known to be present for a number of months before rupture occurred into the subdiaphragmatic space.[385] In such instances intrahepatic infection can be suspected if pain is readily produced by compressing the rib cage over the liver. Acute massive hepatic necrosis can closely resemble the picture of multiple liver abscesses. If an *intermittent biliary tract infection and obstruction* resulting from stones is suspected in an anicteric patient, the demonstration of pus along with cholesterol or bilirubin crystals in the duodenal drainage could be diagnostically decisive.

In only 20 per cent of patients with *subphrenic abscess* is air discernible. This frequently perplexing cause of prolonged fever may follow intra-abdominal inflammation or surgery, extension of an inflammatory reaction from a surrounding organ, or it might represent a metastatic abscess (particularly in children). The diagnosis is more difficult when the process is on the left side, inasmuch as the helpful localizing features on the right are absent. The diagnostic criteria and complications of subphrenic abscess in 139 cases seen in 1942, just prior to the antibiotic era, have been well reviewed and analyzed by Hochberg.[386] The diagnostic use of phrenic nerve stimulation in the patient suspected of harboring a subphrenic abscess is described in Section XVI of Part II (p. 828).

Pelvic abscesses are more prone to give diagnostic difficulties when they are extraperitoneal than when they occur intraperitoneally. The former include cases of inflammation in the prevesical space of Retzius which may result from prostatic abscesses, prolonged indwelling catheters, diverticulitis of the urinary bladder, osteomyelitis of the pelvic bones, or infections

blood cells, "glitter cells (p 708), and positive cultures in the urine[392] In patients with an active pyelonephritis, the peritoneal irritation from the retroperitoneal inflammation can produce a *paralytic ileus* of such magnitude as to require a laparotomy Another complication of urinary tract infection that is infrequently considered relates to the development of *spinal osteomyelitis* This presumably occurs via the numerous anastomoses between the venous plexuses of the pelvic organs and those of the spinal column[393]

NECROTIZING RENAL PAPILLITIS

Physicians are now becoming more aware of the problem of necrotizing renal papillitis in the diabetic who is uremic or severely ill from unexplained cause This is most fortunate, inasmuch as there are often no subjective symptoms or physical signs here to direct attention to an infective process involving the kidneys[394] Unless one is fortunate enough to find a papillary cast, the only way of establishing this diagnosis clinically with any degree of accuracy is by the demonstration of certain findings with careful retrograde pyelographic studies These include ulcerative or erosive papillary changes, intramedullary sinus formation parenchymal cavitation extruded papillae with secondary clublike papillary fossae, ureteral or calyceal obstruction, intrapelvic filling defects, and other less frequent signs[395]

Renal medullary necrosis is also encountered in the presence of urinary tract obstruction This poses a consideration of great importance since the papillitis may be unilateral and therefore potentially curable[396] Spontaneous renal and perirenal emphysema can occur as a result of infection by *Escherichia coli* in patients with poorly controlled diabetes mellitus[399b]

SIGNIFICANCE OF BACTERIURIA

Guze and Beeson have attempted to determine both the reliability and safety of *bladder catheterization*[397] Notwithstanding the employment of a meticulously aseptic and antiseptic technique, they found that small numbers of bacteria were sometimes transferred from the urethral canal into the bladder and could be recovered in cultures of the bladder urine Infection of the urinary tract probably does not occur as often through the lumen of indwelling catheters as it does via the space between the catheter and the urethral mucosa containing as it does a mixture of both urine and exudate that favors bacterial growth The role of contaminated urinals, toilet and washing facilities, nurses hands mattresses blankets, pillows and air and ward dust in the pathogenesis of cross infection with resistant organisms has recently received greater appreciation and has exonerated catheters and cystoscopes to some extent[490b] It has been aptly stated that the long term risk of complications from the catheterization of a diabetic patient approximates that of a thyroidectomy

The problem of reliable urine bacteriologic studies is often a diagnostic thorn Whereas pyuria during a urinary tract infection may be intermittent and variable it has been shown that the presence of a moderate number

that "its outstanding characteristics are indolence and extreme chronicity, [and that] it is not uncommon for this infection to proceed to a stage of severe renal damage without any preceding illness or disability which can be identified in retrospect as having been a manifestation of acute pyelonephritis" Concerning incidence, it is well to bear in mind that chronic pyelonephritis is a much more common finding at autopsy than either chronic glomerulonephritis or benign nephrosclerosis [199] Although the natural course of pyelonephritis is toward healing, even a healed pyelonephritis may result in hypertension or uremia

It should be emphasized that not only are the urinary findings apt to vary considerably from time to time, but that they can be repeatedly normal if the inflammatory process is localized primarily in the interstitial renal tissue, without having established a communication with the tubular system [389] In this regard, Muehrcke and his colleagues have reported upon five patients whose urinary cultures were negative, yet in whom positive bacteriologic cultures were obtained from needle biopsy specimens of the kidney [390]

Since pyelonephritis often follows completely unpredictable courses, it must be actively considered and pursued in the following clinical situations [388, 389]

1 The onset of rapidly progressive hypertensive vascular disease in patients under thirty, particularly when a convincing hypertensive familial background is lacking

2 The presence of renal insufficiency in a hypertensive patient that seems out of proportion to the diastolic blood pressure and retinopathy

3 The presence of a pronounced anemia in malignant hypertension

4 In unexplained chronic renal disease when glomerulonephritis has been ruled out, particularly when there is a marked fluctuation in renal function from time to time (due to the remissions and exacerbations of the underlying infectious process)

5 When a marked acceleration of renal dysfunction occurs in polycystic renal disease, diabetes mellitus, gout, or with disturbances of the bladder innervation especially following previous catheterization

6 The presence of marked disturbances in tubular function *with* subsequent acidosis and the inability to conserve electrolytes, resulting in a variety of disorders (the Lignac Fanconi syndrome, osteomalacia, Milkman's syndrome, "salt losing nephritis," "potassium losing nephritis," secondary hyperparathyroidism, renal rickets, infantilism, and osteosclerosis) (see Chronic Renal Disease under Group II)

7 Recurrent bouts of fever, sweats myalgias, and other nonspecific symptoms

8 The precipitation of anuria or fulminating renal failure during an acute nephritic exacerbation or after catheterization or instrumentation of the urethra, bladder, or ureters [391]

Pyelonephritis may masquerade as toxemia of pregnancy because of the presence of persistent albuminuria, even when other genitourinary symptoms and signs are completely absent Finnerty has shown the significant *frequency* of this particular situation (in 73 of 1130 patients referred to a toxemia clinic), based primarily on the careful search for clumps of white

necrosis ("lower nephron nephrosis") under the assumption that an exact hour to-hour knowledge of the urinary output is always mandatory If the patient is receiving correct therapy and is carefully observed at frequent intervals, with particular reference to bladder percussion and individual catheterizations, this entire issue can be obviated Next, as much information should be obtained from intravenous pyelography as is possible—even resorting to the use of double doses of the contrast medium and compression techniques—before employing either cystoscopy or retrograde pyelography in instances of obscure minimal hematuria in children and in upper renal tract infections Finally no conscientious clinician should be content with a negative report of the inexperienced laboratory technician in cases of dysuria and pyuria The finding of pus casts in the sediment is so pathognomonic of true renal infection and can be arrived at so readily that all technicians must be properly instructed to report them as such rather than as "clumps of pus cells as is almost always the case (p 707)

Prostatitis and Seminal Vesiculitis

Subacute and chronic nonspecific prostatitis and seminal vesiculitis are sufficiently common to merit serious consideration in the differential diagnosis of obscure fever and atypical pain in the flanks groins buttocks abdomen, perineum and lower extremities in male patients The reader is referred to the paper by Harlin on the little understood and less frequently diagnosed entity of seminal vesiculitis [400a] When a resistant prostatitis seminal vesiculitis urethritis or cystitis affects males, the *Trichomonas* organisms should be sought for in fresh specimens of urine [400b] A feature of seminal vesiculitis that is almost diagnostic is the association of painful emissions with pus or blood in the semen

Acute Hemorrhagic Cystitis Caused by Pleuropneumonia like Organisms

An abacterial pyuria associated with severe urinary bladder symptoms membranous sloughs fever suprapubic and perineal pain, and a poor response to sulfonamides or penicillin may be due to the acute hemorrhagic cystitis caused by pleuropneumonia like organisms (PPLO) [401] It is felt that this infection is frequently transmitted venereally in view of its predominant incidence among promiscuous males Not only may there be an associated nongonococcal urethritis epididymitis and prostatitis but also a conjunctivitis arthritis and changes in the skin (erythema nodosum herpes simplex a generalized papular eruption keratodermia blenorrhagica) This symprom complex at once suggests a common denominator with Reiter s disease Fortunately these organisms are usually sensitive to streptomycin and the tetracyclines Doubt still exists in some quarters however concerning the clinical significance of finding PPLO

ACUTE AND SUBACUTE BACTERIAL ENDOCARDITIS

The problem of acute and subacute bacterial endocarditis bears constant re-emphasis since this diagnosis still frequently comes as a complete

of bacteria on a stained smear of freshly voided urine is highly suggestive of *significant bacteriuria* In fact, an increasing number of laboratories are now utilizing quantitative bacterial counts using either the direct method or the agar pour plate technique as part of their routine procedure in urinalysis and urine cultures The presence of 10,000 to 100,000 viable organisms per ml of urine is almost certainly indicative of infection—usually that of a pyelonephritis with hydronephrosis—whereas the finding of 1000 to 2000 per ml (in the absence of treatment) is quite suggestive of contamination[393] Since pyuria azotemia albuminuria, or the presence of granular casts are not reliable indices of the presence or absence of active pyelonephritis the finding of more than 100,000 bacteria per ml assumes even greater significance[395b]

The use of these methods may help to identify clinically a large segment of the numerous patients with pyelonephritis who would otherwise be diagnosed only at autopsy This is particularly important in the case of women The finding of single or multiple bacterial species in the urine cultures is often of added import Whereas pure cultures are found in from 80 to 100 per cent of patients with acute pyelonephritis, the incidence drops to as low as 20 per cent when there are complicating structural abnormalities in the urinary tract[399a] Infection with such urea splitters as *Proteus* and the *Staphylococcus* often introduces the additional complication of (phosphate) renal calculi It is hardly superfluous to point out that guinea pig inoculation is always in order in the presence of pyuria and repeatedly negative urine cultures (See Section III of Part II)

In the light of the previous discussion, it is apparent that there is an urgent need for both a reappraisal and correction of a number of misconceptions and practices that have a direct bearing upon the problem of pyelonephritis This is the universal conclusion of Kass, Schwartz, and others who have made great contributions to our knowledge of this disease First, the clinician must reorient his attitude concerning the significance of 'lower urinary tract infections," especially in females, as manifested by local bladder and urethral symptoms Very frequently, they have been indicative of actual interstitial renal infection Secondly, a re-evaluation of the need for routine (and at times indiscriminate) catheterization for the collection of urine specimens for cultures and for preoperative and postoperative or prepartum and postpartum care must be forthcoming in medical and surgical practice alike Even in females, there is very little increase in the number of contaminant organisms as shown by quantitative colony counts, when clean voided urine specimens are taken after careful local preparation of the vulva The potential hazards of iatrogenic urinary tract infection are compounded in the surgical or obstetric patient who already has pre-existing impaired renal function or poor bladder function These individuals are not infrequently thrown into severe acute uremia by such manipulations This problem can be surmounted to some extent by the direct aspiration of urine from the bladder after the abdomen has been opened and by the emphasis on individual and very few postoperative catheterizations

Physicians are particularly prone to err by the almost reflex impulsiveness to catheterize the patient who is suffering from acute renal tubular

ous cardiac medications (quinidine, procaine amide, the mercurial diuretics) have been encountered, but not to digitalis the appearance of fever, petechiae, and splenomegaly in response to quinidine was observed by the authors cited above [403b]

3 *Embolism not due to endocarditis*—some reserve must be exercised in the patient with valvular heart disease who evidences such lesions as petechial hemorrhages, retinal vessel embolism, and "splinter hemorrhages" under the nails before unequivocally committing the patient to the diagnosis of bacterial endocarditis, all experienced clinicians have encountered exceptions to this usually correct deduction, the following instances deserve mention in this regard—the aforementioned hemorrhagic and embolic phenomena have been observed along with hematuria and Roth's spots in the retina in patients dying of a rheumatic carditis, in active rheumatic fever and in the postcommissurotomy syndrome [403b, c] these lesions might be the result of such diverse causes as injury to the nail beds, poorly fitting dentures drug reactions (with or without a thrombocytopenia), the local rheumatic vasculitis, or sterile embolization from either a rheumatic valvulitis or fibrillating atria the diverse manners in which pulmonary embolism might present itself (fever tachycardia, recurrent pneumonitis, progressive heart failure) could also be confused with bacterial endocarditis (p 212)

4 *Splenomegaly not due to endocarditis*—there are many reports in the literature which confirm the tenet that splenomegaly can occur in patients with rheumatic heart disease who do not have an endocarditis, even in the absence of congestive failure or splenic infarction [403d]

5 *Systemic lupus erythematosus*—the marked similarity of this disease to both rheumatic fever and bacterial endocarditis will be subsequently considered (p 304) it is pointed out however, that the latter infection can become superimposed upon the valvulitis produced by lupus erythematosus [338]

6 *Hemoglobin pneumonia*—in addition to the pulmonary changes produced by pulmonary vasculitis pulmonary infarction, or rheumatic pneumonitis (p 232) that might complicate the course of the patient with rheumatic heart disease this particular entity deserves some attention the disorder is initiated by a bronchial hemorrhage in patients with mitral stenosis which is then followed by the aspiration of blood into the lung, physical and radiographic signs of this process are not always present clinically, it is characterized by fever tachycardia leukocytosis and apprehension—usually coming in the form of attacks at night [407b, c] They tend to follow unusual activity during the preceding day As in the case of pulmonary infarction there may be an ensuing icterus

7 *Ball valve tumors of the heart*—the ability of this disorder to produce fever heart murmurs (at times highly suggestive of mitral stenosis), and multiple peripheral embolism should be borne in mind this entity will be considered at greater length in a subsequent chapter (p 257)

While the mitral valve most often represents the seat of the bacterial invasion an *aortic valve endocarditis* is not infrequently found to be the cause of unexplained fever particularly in the elderly [406a] In a comprehensive study of 83 patients with rheumatic heart disease and severe aortic

surprise to attending physicians at postmortem examinations, even when the heart murmur and fever were present clinically The major source of error often arises from the focusing of attention on some single symptom or organ (usually other than the heart) which has become secondarily involved

These *manifestations* of bacterial endocarditis may include subarachnoid hemorrhage, meningeal irritation, hemiplegia, a toxic organic psychosis, pulmonary infection, congestive heart failure, diffuse glomerulonephritis clubbing of the fingers, renal failure, and very often a severe unexplained anemia[403 405] In addition to the anemia and leukocytosis, Daland and her colleagues have stressed the predominance of histiocytes in blood drawn from the ear lobe (due to the greater selective filtering capacity of the vascular bed there), and the striking granulocytosis with heavy toxic granulation of the neutrophiles[405b] On several occasions, a profound leukopenia has accompanied the endocarditis[409b] Thrombophlebitis and gastrointestinal bleeding occur very infrequently in endocarditis

The cutaneous lesions of subacute bacterial endocarditis that have been described are legion They *include* petechiae purpura erythematous nodules, circinate eruptions and splinter hemorrhages There may be considerable difficulty in clearly distinguishing between the arthropathy and the myocarditis of this disease and that of active rheumatic fever A history of recurrent febrile symptoms following the cessation of inadequate antibiotic therapy is characteristic of endocarditis Concerning the prophylaxis of this complication in patients with rheumatic heart disease, sufficient attention has not been paid to the relatively simple local antibiotic methods for the reduction of the oral bacterial flora prior to dental extractions

Splinter hemorrhages in the nails are depicted in Figure 32 (Atlas page 21)

A dilemma in differential diagnosis that frequently confronts the consultant physician occurs in the form of *coexisting fever and valvular heart disease* While a bacterial endocarditis must obviously receive the foremost consideration in such a situation and should never be minimized, there are other conditions in which fever may develop in the presence of a concomitant involvement of the heart valves The experiences of Ross McKusick and Harvey in their review of this problem should be studied by all clinicians[403b] The following considerations (modified after the differential diagnosis set forth by these authors) while far from complete are helpful for purposes of orientation

1 *Active rheumatic fever*—this problem is compounded by the frequency with which false-positive and false-negative blood culture reports occur (*vide infra*) the clinical axiom that bacterial endocarditis does not develop in patients with auricular fibrillation must be regarded in the light of the many exceptions to this rule of thumb the clinical response of patients to aspirin (p 814) or the antibiotics in the form of a therapeutic diagnostic test is attended by a number of potential pitfalls in the differentiation of bacterial endocarditis and active rheumatic fever

2 *Drug fevers*—the serum sickness type of reaction to penicillin can closely mimic active rheumatic fever (p 310) febrile reactions to the vari

invasion, particularly *Streptococcus pyogenes* *S mitis*, and *S faecalis*[412] It is recognized with less frequency now, however, since the widespread use of antibiotic therapy In certain patients with overwhelming bacteremia (staphylococcal enterocolitis pneumonia in alcoholics or in the aged, urinary tract infections, contaminated blood), there is often a resulting intense vasoconstriction along with marked cardiac damage This differs from the usual response of most patients so that the existence of a severe primary infection may not be readily appreciated if blood cultures are not taken

Mycotic endocarditis cannot be differentiated from bacterial endocarditis on clinical grounds alone Consequently, the finding of fungi (particularly *Cryptococcus neoformans* and *Candida albicans*) in cultures obtained from patients suspected of having subacute bacterial endocarditis should not be dismissed too hastily as contaminants In one review of this subject, four of 10 patients with a *Candida* endocarditis were drug addicts eight of whom had one or more positive blood cultures[41]

In the presence of a subacute bacterial endocarditis with severe pain in the left upper quadrant of the abdomen a pleural reaction on the left, and a continuous bacteremia in spite of large doses of antibiotics one should suspect *infection in a splenic infarct* This might prove to be a life-saving consideration inasmuch as a complete remission has followed splenectomy in these selected cases[413]

In the presence of a valvular lesion or a congenital abnormality (particularly a patent ductus arteriosus and high interventricular septal defects) fever, pulmonary infarction splenomegaly, and repeatedly sterile blood cultures attention should be directed towards a *right sided bacterial endocarditis*[414a] The tricuspid valve appears to be more susceptible to invasion than the pulmonic valve An endocarditis affecting primarily the right side of the heart—and more specifically the tricuspid valve—should also be entertained in the presence of a triad consisting of opiate addiction (heroin) septicemia (often due to antibiotic resistant staphylococci), and radiographic evidence of pulmonary infarctions in the absence of a peripheral phlebitis[414b] *Many clinicians have independently observed that* endocarditis rarely occurs in the patient with an uncomplicated interatrial septal defect

Prolonged sepsis negative blood cultures and a subsequent hemothorax or hemopericardium in the patient with a myocardial infarction should suggest a *septic thrombus* or an *infected aneurysm with perforation*[415]

Endocarditis is often a *complication of the advanced phases of cancer* This lesion is usually related to the degree of necrosis of the tumor and the subsequent ulceration with secondary infection The presence of an acute hemiplegia in a patient with terminal cancer should therefore direct attention to the possibility of a bacterial invasion of the heart valves[416]

Aseptic thrombotic vegetations are also encountered under similar circumstances[417] MacDonald and Robbins have reviewed 78 cases of *nonbacterial thrombotic endocarditis*[417] Embolization was the main clinical manifestation, resulting from the breaking off of a portion of the adherent thrombus this complication contributed to the patient s demise in 11 instances The aforementioned authors point out that the predominant soil upon which these thrombi form is the nonspecific focal fibrocollagenous de-

insufficiency, a 22 per cent incidence of bacterial endocarditis was observed [407] In fact, the manifestations of severe aortic insufficiency and rapid congestive failure first became apparent or aggravated in over half of these cases following this complication Bicuspid aortic valves (which occur in up to 40 per cent of patients with coarctation) are likely to be the basis for murmurless bacterial endocarditis [406b 420d]

The predilection of the pneumococcus for localization upon aortic valves which are either normal or previously diseased, and the relative frequency with which the right side of the heart is involved have been long appreciated Austrian observed the syndrome of pneumococcal endocarditis, meningitis and rupture of the aortic valve in one fifth of the patients with pneumococcal meningitis that he encountered within the past decade [406c]

It should also be noted that an occasional patient may exhibit *no murmur* if specific therapy is administered (or if death occurs) before the valves have actually become ulcerated There are instances on record of such minimal gross changes produced by an acute endocarditis affecting a previously normal valve—in which any vegetations that had been present were swept away as emboli—that the definitive diagnosis could be established only by histologic study [409c] This is also true when the vegetations are localized on the aortic wall without a true endocarditis being present, or if they occur on the aortic valves below the line of closure and grow downward toward the mitral valve The gonococcus and the pneumococcus are particularly prone to behave in this fashion although by far the majority of these cases will in time exhibit significant murmurs and valvular destruction [408]

Other instances in which no murmur may be heard include endocarditis arising in mural thrombi following a myocardial infarction (p 272) and the occurrence of vegetations on an atheromatous plaque in the aorta itself [409] In many instances however the murmur has probably not been distinctly heard because of the concomitant noises emanating from the lungs

In regard to *blood cultures* Finland has stated that 97 per cent of the positive cultures can be obtained within the first two days [410] Newman and his colleagues have observed that when a positive blood culture was obtained, it practically always appeared in at least one of the first four cultures taken [411a] Similarly Belli and Waibren found a positive blood culture within the first five cultures drawn in 77 of 82 cases of bacterial endocarditis [411b] Consequently one can justifiably wait these two days to get the necessary repeated blood specimens—*even when the patient is* severely ill—before being forced to initiate therapy This is far from an academic *consideration since a much better recovery rate* is consistently noted in those patients from whom a positive culture can be obtained [410] (See Blood Cultures under Section VI of Part II) Once an aortic valve endocarditis is diagnosed however intensive therapy may be started within twenty four hours because of the danger of a ruptured cusp and the ensuing intractable heart failure [410b]

Unequivocal bacteremia (two or more positive blood cultures) *in the absence of an endocarditis* is most likely to be caused by a streptococcal

cally all of these cases reported, the aortic valve was involved When only an endarteritis exists, the clinical features are similar to those of a bacterial endocarditis, with the exception that there are no peripheral embolic phenomena Consequently, the demonstration of a new heart murmur or hemorrhages in the nail beds or retina suggests a complicating endocarditis

The infecting organism has been the *Streptococcus viridans* in the majority of these cases Attention is called to the observation that numerous cultures may be negative if the venipunctures are made in the antecubital veins but might yield the infecting organism if the blood is taken from the femoral vein proximal to the fistula [4, 1b] Experience has shown that cure cannot be achieved in most instances unless surgical excision of the infected aneurysm is accomplished, either with or without the added help of antibiotic agents

PNEUMONIA OR PNEUMONITIS OF OBSCURE ETIOLOGY

Every experienced clinician has witnessed a sufficient number of un usual cases of pneumonia or pneumonitis throughout the years to appreciate the wide variety of infections, neoplasms, and vascular, cardiac allergic renal and physical disorders that may either manifest themselves in this way or simulate pulmonary illness This orientation has also evolved in some measure from the widespread use of the antibiotic and chemotherapeutic agents Inasmuch as many of the diseases in question do not respond to this type of therapy they can now be separated from the ordinary pneumonias much earlier

The same etiologic implications should also apply to the various con ditions lowering the body s immunologic defenses which are discussed later in this chapter To cite one illustration any child who evidences bronchiec tasis of an undetermined etiology and who is being considered for resectional surgery ought to have the benefit of the relatively simple diagnostic procedures for cystic fibrosis of the pancreas that are presently available (p 48) [185b] Combined pulmonary and abdominal epsis should alert the *clinician to the possibilities of tuberculosis actinomycosis and amebiasis*

The diagnostic errors that are continually made with regard to pul monary tuberculosis—both in a positive and negative manner—probably point out the potential diagnostic traps which clinicians might encounter more so than with any other affliction of the lungs For example during a recent three year period (1952–1954) a consistent average of 18 per cent among 3422 patients who were admitted to the Fitzsimons Army Hospital for an original diagnosis of pulmonary tuberculosis proved to have nontuberculous disease [535a] The following top ten" compri ed 77 per cent of these pseudophthisic disorders encountered and merit repetition according to their relative incidence pulmonary fibrosis pneumonia, bronchiectasis histoplasmosis, coccidioidomycosis pleurisy, malignant neoplasm sarcoid osis granuloma (etiology undetermined) and lung abscess The 12 per cent incidence of fal e-positive sputum reports in this series is rather sobering On the other hand, even the radiographic diagnosis of pulmonary tuberculosis leaves some room for improvement when one considers that only two thirds of the pulmonary area is visualized and that the incidence

generation of the valves of the arteriosclerotic heart Of added interest are the several cases with healed and degenerative types of this disorder that were encountered It is apparent that this diagnosis should be made with great reservation in the presence of rheumatic heart disease

Although only a few instances have been reported, it behooves all surgeons and cardiologists to anticipate with vigorous combined antibiotic therapy an *endocarditis following mitral or aortic valve surgery, ligation of a patent ductus*, and *other types of cardiac surgery* due to the unavoidable breaks in sterile technique[418] An increasing number of cases of staphylococcic endocarditis occurring within one week to three months of a mitral valvulotomy are being observed[419] This complication may be manifest primarily by unexplained fever and malaise In seven such cases, none of the classic signs of endocarditis (petechiae splenomegaly, clubbing of the fingers) could be found In fact, five were treated with anticoagulants because of a presumed pulmonary infarction[419] This problem is considered at greater length under Group XV (p 440)

In view of the readiness with which the infection can be controlled in most cases of bacterial endocarditis the clinician must now take into consideration a number of *other complicating factors and unusual sequelae of healed bacterial endocarditis* when confronted by the intensively treated patient with this disease who is doing poorly These complications include severe myocarditis with heart failure, cerebrovascular accidents embolism, renal failure and aneurysm formation

When a subacute or chronic endocarditis is engrafted upon a normal valve and has been treated with some degree of success, the attending physician may be unable to discount the presence of an underlying rheumatic or syphilitic process[410b] Sufficient damage to (and even rupture of) the chordae tendineae can take place in a case of healed bacterial endocarditis to result in both severe mitral insufficiency and heart failure[427a] The myocarditis and the aggravation of the underlying valvular defect that accompany a bacterial endocarditis can also contribute to the development of congestive heart failure The incidence of heart failure is decidedly proportional to the duration of the untreated endocarditis[410b]

Erosive aneurysms can form on the heart valves and have been encountered with greater frequency since the introduction of the antibiotics They may be of two types (1) thromboaneurysms (or the false aneurysm type) in which the walls of the aneurysm are formed by the vegetations themselves and (2) the true aneurysms which are formed by the endocarditis induced valvular erosion with the walls being composed of the thin walled valve tissue and the vegetations[410c] Once rupture has taken place, however such differentiation is usually impossible Mycotic aneurysms of the various valves or in the aortic sinuses may result in functional stenosis or regurgitation heart failure or a chronic hemorrhagic pericarditis, with or without valvular perforation[420a]

If a patient with an acquired and long standing arteriovenous fistula (usually the result of a previous gunshot wound in the lower extremities) develops an unexplained fever that is not responsive to antibiotic therapy the possibility of a *bacterial endarteritis and secondary endocarditis* must be entertained before the cardiac damage becomes irreversible[421] In practi

careful bacteriologic and serologic studies of the sputum, blood, and pleural effusions are frequently fully as important as the x-ray findings, and must constantly be regarded in this light. The limited manner of the pulmonary response to a wide variety of causes is reflected in the difficulty with which expert radiologists diagnose obscure cases of "miliary" infiltrations, "atypical" pneumonias, and "idiopathic" diffuse fibrosis.[4,5] A similar source of confusion arises in the interpretation of primary pathologic changes and their complications when the abnormality has been modified either by an underlying emphysema or by previous antibiotic therapy. The magnitude of surreptitious self medication for respiratory infections has added considerably to this problem. (See Section VI of Part II concerning bacteriologic and immunologic studies, and Section IX for clinical clues relating to chest x-rays.)

To integrate and supplement the many references to the pulmonary manifestations of disease that have been made throughout this book under the specific disease entities, a differential diagnosis of this highly important subject is now presented in outline form. The reader is also referred to several fine reviews on the subject of the differential diagnosis of diffuse pulmonary lesions and pneumonitis.[4-5, 4-6]

Pneumonitis Due to the Bacteria

Pneumococcus. Suspect an underlying myeloma, lymphoma or hypogammaglobulinemia when recurrent pneumococcal pneumonia occurs in the absence of such local pathologic conditions as bronchiectasis or bronchial obstruction; this organism infrequently causes a severe pharyngitis; the unexplained recrudescence of fever following a previous bout of pneumococcal pneumonia should alert the clinician to the possibility of a pneumococcal endocarditis, especially when concomitant meningeal signs are present;[408c] hypotension, the absence of fever and the presence of leukopenia should alert the clinician to potential dire sequelae in patients with pneumococcal pneumonia, especially in alcoholics and the elderly.

Hemolytic Streptococcus. Suspect this organism when an early serosanguinopurulent pleural effusion complicates a patchy bilateral pneumonia, especially during streptococcal epidemics; it usually begins as a pharyngitis or a tonsillitis; streptococcal pneumonia may complicate measles, pertussis, scarlet fever or even a pneumococcal pneumonia.

Staphylococcus. This infection poses an increasingly common problem, particularly in infants and young children, in pancreatic fibrosis, in the postoperative state and during influenza epidemics; it may result from either superinfection or an acquired resistance to the antibiotics; it is usually a descending infection which can lead to abscess formation in the parabronchial areas; multiple metastatic pulmonary abscesses also may complicate a staphylococcal pyemia; a staphylococcal pneumonitis and empyema are suggested radiographically by the following signs: the occurrence of spontaneous pneumothorax, the development of pneumatoceles, rapidly changing infiltrations with parafocal emphysema, and the early loculation of a pleural exudate.[4-8]

Hemophilus Influenzae Bacillus. This infection may follow a severe

of error in the interpretation of chest films by radiologists can approach 20 to 30 per cent

No clinician should need to be reminded of the importance of ruling out an underlying bronchial obstruction, bronchiectasis, tuberculosis, or neoplasm in the presence of *recurrent pneumonitis* A similar admonition applies to the follow up of every case of '*atypical pneumonia*' *until he is* satisfied that complete clearing has actually occurred *If the patient with* a radiographic diagnosis of 'virus pneumonia' promptly clears on antibiotic therapy and has subsequent symptoms a lung malignancy must be *suspected This is particularly true when the pneumonitis occurs out of* the respiratory infection seasons and when persistent local chest pain is a prominent symptom

Israel and his colleagues have reviewed the important subject of *delayed or incomplete resolution of bacterial pneumonia*, and have also presented a satisfactory time-guided approach to this problem[43] The latter is desirable in an attempt on the one hand to expedite the diagnosis of an underlying neoplasm, abscess, or other pathologic pulmonary state which merits surgical intervention, while avoiding the practice that is becoming more frequent in teaching hospitals with active thoracic surgical services of exploring most patients with a chronic organizing pneumonia[44] Normal resolution is regarded as having occurred when the roentgenograms show complete or almost complete healing four weeks after the onset of a pneumonitis Delayed resolution is indicated by the presence of abnormal chest films at four weeks, but with almost complete clearing having taken place by the eighth week In one series of 139 cases of pneumonia studied at the Philadelphia General Hospital, delayed resolution was encountered in 13 per cent[43] Age and constitutional disturbances relating to nutritional metabolic, and immunologic derangements were often of greater importance than local factors and unusual pathogens in these instances Fortunately such cases of bacterial pneumonia are infrequently the prime cause of permanent pulmonary damage

In the presence of delayed healing thoracotomy should be deferred in most instances when the pneumonitis was initiated by the typical symptoms of pneumonia and if repeated bronchoscopic and cytologic studies are not revealing When an acute history is not forthcoming in individuals over the age of forty under these same circumstances the recommendation of surgical intervention is often reasonable The differentiation between a partial collapse and delayed resolution of the right upper lobe after bacterial pneumonia and a bronchogenic carcinoma may be particularly difficult on clinical grounds alone in some instances Exploratory thoracotomy should be avoided in such a situation when the following features apply the presence of alcoholism the absence of significant respiratory symptoms before the acute illness the sudden onset of widespread bacterial pneumonia involving at least two segments of the right upper lobe, and the aforementioned negative bronchoscopy and negative cytology, along with relatively normal bronchograms[45a]

The value of the physician *himself* studying a specimen of freshly expectorated sputum cannot be overemphasized in the evaluation of an "atypical" pneumonia The necessity for a detailed history along with

the diagnosis of this disease, pleural effusions and enlarged mediastinal nodes commonly occur, agglutinins are almost always present by the third week [432]

Brucellosis Suspect this diagnosis in farmers ranchers and packing house workers who demonstrate either undiagnosed bronchitis or bronchopneumonia or chronic perihilar thickening and peribronchial infiltrations in a recent review of 41 cases of "pulmonary brucellosis," Greer has emphasized the universal lack of awareness of this form of the disease (p 156) [433A]

Typhoid Fever One third of these patients have a significant pneumonitis or tracheobronchitis concomitant "O' and 'H titers of 1 80 or above might signify a true typhoid infection, sporadic cases are more apt to occur in the rural areas [434]

Other Gram negative Bacilli An *Escherichia coli* pneumonia usually represents an aspiration complication pulmonary involvement by *Salmonella Proteus Pseudomonas*, and *Bacteroides* is increasing as a result of either antibiotic resistance or superinfection, particularly in the very young and old Saphra and Winter have reported on 85 patients with *Salmonella* infection of the respiratory system which usually occurs in the form of a lobar or bronchopneumonia in elderly individuals or in patients with hypertension, diabetes mellitus malnutrition, anemia cancer, or other debilitating diseases [59] many of the sporadic infections are caused by *Salmonella choleraesuis*, the history of the snuff habit may shed considerable light on the cause of a chronic bronchitis or a chronic bronchiectasis when the flora of the sputum contains such pathogens as *Proteus vulgaris* and *Pseudomonas aeruginosa* many preparations of snuff having been found to harbor these organisms [4 7] the problem of superinfection with gram-negative organisms is of most concern in respirator polio cases and in those patients with chronic bronchopulmonary suppuration who were given prophylactic antibiotics (p 138)

Meningococcus A lobar pneumonia due to this organism has been noted on rare occasions it can take place in the absence of a meningitis or a purpuric rash [572] since it may occur concomitantly with a pneumococcus the meningococcus is apt to be overlooked if proper cultures are not taken (p 136)

Plague The possibility of plague should concern the clinician when a fulminant pneumonia or septicemia affects men who have been working around rat infested ships coming from infected ports while pneumonic plague has not been observed in this country, sylvatic plague does exist the *Pasteurella pestis* can be isolated from the sputum either by culture or by inoculation of guinea pigs

Anthrax A pneumonic form of this disease may be acquired by individuals who handle such spore-infected material as wool animal hair, and hides

Chronic Systemic Melioidosis This disorder is rare in the United States with most of the reported cases having occurred in the Far East or in the Pacific islands the lung is the organ that is most frequently involved with the clinical picture resembling that of a disseminated fungus infection or tuberculosis the pathologic changes are extensive sharply de-

laryngotracheobronchitis in young children, especially pertussis, or it may complicate an underlying chronic bronchopulmonary infection in adults, it is a common superinfecting organism following antibiotic therapy, detection of the influenza bacillus can be overlooked if only routine blood enriched media for bacterial growth is employed, there has been a tendency to minimize the pathogenicity of the nonencapsulated *H influenzae* organisms in the mucous membranes of the bronchial tree, especially in children with bronchiectasis[430b]

Friedlander's Bacillus Suspect this organism in the aged or in malnourished alcoholics who exhibit early severe prostration with bloody gelatinous sputum, upper lobe involvement bulging of the interlobar septum and rapid necrosis with abscess formation, a typhoid like picture and the development of metastatic abscesses may also occur, characteristic large mucoid, pearly colonies are produced when cultured on blood agar,[4 4] while *Klebsiella* infection is characterized by a tendency to delayed resolution, chronicity, residual cavitation and fibrosis, this organism is occasionally present as a nonpathogenic bacteria in the sputum of individuals without respiratory disease, it may also give rise to a superinfection, a number of studies have called attention to the fact that *Klebsiella pneumoniae* and *Aerobacter aerogenes* cannot be distinguished on any basis,[4 9] since pulmonary tuberculosis may concomitantly be present in the patient with Friedlander's pneumonia it is advisable to submit a specimen of the sputum for culture of tubercle bacilli prior to initiating streptomycin therapy[429b]

Pertussis Although this disease is milder, less common, and often atypical in adults it deserves attention in the diagnosis of a persistent severe bronchitis with paroxysms and a significant lymphocytosis, this lacl of immunity after childhood is most apt to be manifest in individuals coming from rural areas particularly during periods of military mobilization,[430a] in addition to the significant incidenc of superinfection and central nervous system complications pertussis may activate a case of latent pulmonary tuberculosis

Tuberculosis Always suspect this diagnosis in any atypical nonresolving pneumonia or in the presence of an unexplained pleural effusion particularly when affecting Negroes and other susceptible races diabetics and patients who are on steroid therapy,[431] primary 'childhood infection complexes may also be encountered in adults who had previously been tuberculin negative since early adult type pulmonary tuberculosis is limited solely to the anterior segment of an upper lobe only on rare occasions, the finding of such a lesion in itself should compel the clinician to consider other etiologic possibilities,[346] the diagnostic value of tuberculin testing the liver biopsy, and marrow aspiration studies is stressed under Group V, only careful bacteriologic analysis can differentiate tubercle bacilli from the saprophytic acid fast bacilli (p 153)

Tularemia Suspect this diagnosis when a pneumonitis follows contact with ticks and various animals especially wild rabbits, the pulmonic form may be the only manifestation of visceral involvement, particularly in the so-called typhoidal type the presence of cutaneous ulcerations and an associated peripheral lymphadenopathy is obviously of great value in

strated in four, while an amebic bronchitis was present in one patient without any demonstrable liver involvement (p 171)

Visceral Roundworm Dissemination Suspect ascariasis, hookworm disease, and visceral larva migrans in the presence of unexplained pneumonitis and eosinophilia (p 173)

Trichinosis Symptoms may be referable either to the larval migration through the lungs, or to the involvement of the respiratory muscles (p 173)

Pneumonitis Due to the Viral and Rickettsial Agents

These diseases as a rule produce very similar clinical and radiographic features herpes simplex and pleural effusions are uncommon complications[438]

"Primary Atypical Pneumonia" This disease may be accompanied by a meningoencephalitis or by a hemolytic anemia following the use of alcohol rubs or other chilling procedures[439] this infection can be confused with tuberculosis because of the persistent infiltration in an upper lobe, or with heart failure in the elderly in most cases the antibiotics produce but little effect on the blood changes the cold isohemagglutination titer, the x ray findings or the actual duration of this pneumonitis[440]

Influenza Sporadic cases can be suspected only by their fulminant course and by viral studies bacterial superinfection is common, particularly with the *Staphylococcus*

Ornithosis psittacosis Suspect these diagnoses if the patient has been exposed to parakeets or has handled poultry it may be accompanied by splenomegaly, thrombophlebitis and a typhoid like picture (p 161)

Varicella The pneumonitis tends to be very severe in adults it is manifested by dyspnea cyanosis hemoptysis and diffuse infiltrations occurring two to four days after the rash this infection may also follow exposure to herpes zoster a secondary bacterial invasion—especially with the *Staphylococcus*—can usually be found to explain the pulmonary complications of chickenpox in children other complications of varicella pneumonia have included massive nonbacterial pleural effusion, subcutaneous emphysema and pulmonary edema it is very important to differentiate this complication from smallpox miliary tuberculosis influenza and erythema multiforme exudativum the characteristic large giant cells found in the cutaneous vesicles can help in this differentiation[441]

Infectious Mononucleosis This diagnosis may not be suspected in the presence of a pneumonitis with or without a concomitant pleural effusion until the characteristic virocytes and heterophile response are found (p 743)

Q Fever Suspect this diagnosis in dairy cattle and sheep workers who exhibit atypical pneumonia second attacks and pleural effusions can occur if no prompt response to the tetracyclines ensues or if no antibody rise occurs after four weeks, the accuracy of this diagnosis is dubious[44] significant hepatitis splenomegaly or obscure fever may be present with little pulmonary involvement[339] since *Coxiella burnetii* can survive in

fined, and minute abscesses containing caseous pus and surrounded by granulomatous margins, the etiologic organism, *Malleomyces pseudomallei*, is a motile, bipolar staining gram negative bacillus, it may not be found in either the sputum or the resected lung specimen, however, in which case the diagnosis of 'granulomatous pneumonitis, cause undetermined' has been made the diagnosis may also be arrived at by an agglutination test the complement fixation test or the Straus reaction (in which an acute peritonitis and orchitis develop in male guinea pigs into whom the pus is injected) the disease is apparently spread by food contaminated with rat excreta but has also been transmitted by injection in morphine addicts [550]

Pneumonitis Due to the Systemic Mycoses and Parasites

Histoplasmosis Suspect the subacute stage of this illness when extensive pneumonitis adenopathy, ulcerations of the upper gastrointestinal tract and hepatosplenomegaly occur in endemic areas, particularly following exposure to such closed areas as silos and cellars, in the presence of undiagnosed pulmonary infiltrations be sure to check the histoplasmin skin test if the tuberculin test is negative with prolonged observation, the development of specific serum antibodies for *Histoplasma capsulatum* and miliary calcification is diagnostic (p 167) [435]

Coccidioidomycosis Suspect this infection when persistent miliary or other pulmonary lesions—particularly thin walled cavities—and hilar adenopathy are found in the presence of a negative tuberculin test do not overlook a concomitant bronchogenic carcinoma or tuberculosis which may be readily masked roentgenographically by the residua of this disease (p 166) [436]

Moniliasis The entity of primary pulmonary moniliasis is rare even with the current extensive use of antibiotics this diagnosis is *not* justified solely on the basis of demonstrating the organism in the sputum, a pleural effusion due to this organism may occur

Blastomycosis The sputum is usually positive when abscesses in the skin subcutaneous tissues and the bones exist even in the absence of chest symptoms the skin test is positive in only half of the cases, it may closely simulate both pulmonary neoplasms and tuberculosis (p 167)

Actinomycosis Suspect this diagnosis when massive bilateral consolidation particularly of the lower lobes is complicated by draining sinuses and abdominal manifestations see Group V concerning the importance of its differentiation from nocardiosis (p 168)

Torulosis Pulmonary involvement in this disease may be asymptomatic or it may simulate tuberculosis and the other mycoses always look for an underlying lymphoma or a concomitant meningitis once this diagnosis is made (p 167)

Amebiasis An amebic liver abscess can simulate a pneumonia or lung mass, or it may produce an empyema with a bronchopleural fistula exuding the characteristic thick chocolate colored material Webster substantiated the diagnosis of pulmonary amebiasis in six of 95 patients with intestinal amebiasis by the demonstration of *Entamoeba histolytica* trophozoites in the sputum [437] a bronchobiliary communication could be demon

anthrasilicosis, the symptoms and mortality are due chiefly to the concomitant emphysema and cor pulmonale [444a]

SILICOSIS Free crystalline silica of fine particle size must be inhaled, the tuberculosis diathesis is significant

ASBESTOSIS An increased tendency to malignancy and extensive fibrosis exists in this disease [444b, c]

SIDEROSIS Iron oxide

BAGASSOSIS Sugar cane fibers

BYSSINOSIS Cotton fiber dusts

SHAVER'S DISEASE Aluminum bauxite abrasives

TALC PNEUMOCONIOSIS May also be associated with pericardial calcification [848a]

CALCINED DIATOMACEOUS EARTH

Berylliosis See discussion under Group VII (p 206)

"Silo-filler s Disease" This severe disorder has been observed in individuals who have entered silos within a week after the silos were filled with corn silage, it is probably due to nitrogen dioxide which causes an early pulmonary edema and a subsequent bronchiolitis fibrosa obliterans with numerous discrete nodular densities [445]

Metal fume Fever This is a distinct self limited but disabling occupational disorder that is frequently labeled as "influenza or "grippe' it most commonly results from the inhalation of zinc oxide fumes as may occur in smelting, galvanizing brass-founding brazing and oxyacetylene welding of galvanized iron other metals have also been incriminated complete recovery is usually evident by the second or third day [446]

Radiation Pneumonitis The fibrotic process may be indistinguishable from idiopathic pulmonary fibrosis suspect such a process when atypical chest symptoms or x ray findings occur in the lung underlying an area that was previously subjected to radiation therapy most notably for carcinoma of the breast (p 398) [1198, 1200] a severe and potentially fatal radiation pneumonitis and fibrosis has occurred in patients with cancer of the thyroid and pulmonary metastases due to this neoplasm who have been given large doses of radioiodine [1198d]

Lipoid Pneumonitis Suspect this diagnosis in the presence of a chronic pneumonitis affecting elderly people with poor gag reflexes who habitually consume mineral oil unlike malignancy it tends to extend peripherally and does not produce a hilar adenopathy or atelectasis the superior segments of the lower lobe are most commonly affected when oily nose drops are used whereas the course of an oil aspiration pneumonia is often acute and fatal in children, the picture and prognosis are usually quite different in adults [447]

Aspiration Pneumonitis One should suspect an underlying esophageal diverticulum or cardiospasm in the patient with unexplained recurrent pneumonitis [448] gram negative bacilli are commonly responsible the periodic and unrecognized transadital aspiration of material from the esophagus in a variety of other disorders affecting this organ in which there is retention or transcardial reflux (hiatal hernia, carcinoma, stricture due to lye or radiation) commonly results in chronic pulmonary disease in addition to chronic bronchitis and recurrent pneumonia, chronic pul

milk that has been pasteurized, Q fever might be encountered in milk drinkers

Other Rickettsioses The pneumonitis in the various forms of typhus fever and Rocky Mountain spotted fever usually occurs late, the diagnosis may be verified serologically after being suspected because of the cutaneous lesions or the epidemiologic circumstances, consolidation is unusual, however (p 162)

Erythema Exudativum Multiforme, the Mucocutaneous Ocular Syndromes, the Stevens Johnson Syndrome In 20 to 30 per cent of these patients, a pneumonitis occurs which may be indistinguishable from primary atypical pneumonia clinically, serologically, and radiologically [336c] the pulmonary changes may be very slight, or they may result in the almost total consolidation of both lungs the pneumonitis is most likely a further manifestation of the injury to the mucous membranes of the tracheobronchial tree, this disease will be described in further detail in the next chapter (p 161)

Pneumonitis Due to the Allergic and Collagen Diseases

See Groups II and X for a detailed discussion of the individual entities serum sickness and hypersensitivity reactions (p 62), [225] Loffler's syndrome (p 64) [224] rheumatic fever (p 310), [3 3] malignant rheumatoid arthritis (p 312)[974, 973] (the association of massive pulmonary fibrosis and rheumatoid arthritis has been described under the designation of Caplan s syndrome), lupus erythematosus (p 305) [332] polyarteritis (p 307) [943] scleroderma (p 309),[959, 963, 987] erythema nodosum (p 313) [980, 982]

Pneumonitis Due to the Granulomatous Disorders

See Group VII for clinical clues to the individual entities sarcoidosis (p 204),[742, 745] Wegener s granulomatosis (p 206) [757, 759] chronic pneumonitis of the cholesterol type (p 207) [451] Chronic pneumonitis of the cholesterol type has been observed both in the presence and absence of bronchial obstruction [451c]

The Histiocytic Reticuloendothelioses X ray surveys of the entire skeleton should be performed in all young adults and children who are found to have chronic diffuse pulmonary fibrosis and an 'alveolar capillary block" because of the possibility of an underlying Hand Schuller Christian disease—also referred to as disseminated histiocytosis X,[765c] similarly "honeycomb lungs may be associated with xanthomatosis and tuberous sclerosis (p 207) [760, 763, 1260]

Pneumonitis Due to Physical Agents

The Pneumoconioses Fever dyspnea and nodulation may be absent in the earlier stages a detailed occupational and hobby history is essential, this term does *not* necessarily imply actual disabling disease and should be used *only* after great deliberation [443] although nontuberculous ischemic cavities occur in approximately 1 per cent of patients with third stage

locular, and centrally or eccentrically placed, it is important not to ascribe these air filled cystic spaces to tuberculosis or to a lung abscess, since they tend to disappear spontaneously within a relatively short period of time and with no significant sequelae

Cardiac, Vascular, and Renal Disorders

Pulmonary Edema Interstitial edema may produce high fever without an underlying infection, this phenomenon is particularly prone to occur within the first week after an acute myocardial infarction and will respond only to diuretic therapy [452] it is also known that patients with pulmonary edema are particularly vulnerable to pneumonia, and are often wisely treated prophylactically for this potential complication,[453] basilar rales and hemoptysis simulating acute pneumonia may on occasion be the first manifestation of heart failure a unilateral left pleural effusion is quite uncommon in cardiac failure, unless the right pleural cavity has been obliterated by adhesions

"Vanishing Tumor of the Lung" This localized interlobar pleural effusion should be suspected in patients who have large hearts and who may be in early heart failure the right transverse fissure is the most frequent site for such an effusion a significant number of these individuals have been subjected to diagnostic thoracotomy for a suspected pulmonary malignancy when this entity was not considered, the prompt disappearance of the density following a course of diuretic therapy will positively establish the diagnosis under these circumstances [83]

Pulmonary Infarction Sharply angular lesions in chest films are highly suspicious of pulmonary infarcts suspect this complication in the presence of increased pulmonary vascular pressure when the patient exhibits chest wall tenderness or jaundice even in the absence of frank embolism the hilar mass and peripheral opacity can occasionally closely simulate a neoplasm [454a] the occurrence of ' pneumonia ' in a known drug addict (especially a heroin addict) should alert the clinician to the possibility of a right sided endocarditis particularly when the x ray densities—which actually represent infarctions—are multiple [414b] a pulmonary infarct can be associated with necrosis and cavitation (p 212) [454b]

Pulmonary Embolism—Sterile Septic or Fat Suspect these diagnoses in pneumonitis occurring postoperatively or postpartum, in drug addicts, and after fractures of the long bones respectively (pp 212 and 216) [414, 456]

Sickle Cell State When atypical pneumonitis or pulmonary infarction occurs in a Negro one should routinely pursue sickle cell studies including paper electrophoresis, irrespective of the existing level of the hemoglobin or hematocrit (p 195) [713b]

Renal Failure The pulmonary congestion and hyaline membrane in uremia may result in a striking ' butterfly roentgenographic appearance closely resembling atypical pneumonia although this pattern of bilaterally symmetrical densities in the central lung fields with comparatively clear peripheral zones is regarded as being specific for the uremic pneumonia by several authors it is frequently not present in renal failure furthermore it may occur in other cardiovascular disorders that are associated with

monary fibrosis, bronchiectasis, lung abscess, and either pneumothorax or empyema due to perforation have been encountered,[443c] this form of pneumonitis is also prone to affect patients with bulbar or pseudobulbar palsy

Hemoglobin Pneumonia It is important to be cognizant of this entity in the patient with mitral stenosis since it might be readily mistaken for a complicating bacterial endocarditis, it results from the aspiration of blood into the pulmonary parenchyma following a bronchial hemorrhage, and is most apt to occur after periods of unusual exertion, clinically, it is characterized by fever, tachycardia, leukocytosis, and apprehension—classically coming in the form of attacks at night the clinician must be aware of the fact that the physical signs and x ray findings may be minimal, since icterus also tends to follow this train of events it may be necessary to differentiate this condition from pulmonary infarction[1035b] *

Obstructive Atelectasis The pneumonitis complicating asthma, emphysema or fibrocystic disease is apt to be particularly serious, foreign bodies must always be considered in the presence of atypical pneumonia or asthma affecting children and infants

Mucoid Impaction of the Bronchi The occurrence of x ray shadows variously resembling a V shape or the appearance of a cluster of grapes —along with fever hemoptysis, and chest pain in the patient with asthma or obstructive bronchitis—suggests this condition, the unique predilection for the upper lobes in the five cases reported by Greer and in nine out of the 10 cases reported by Shaw helps to distinguish this entity from the usual variety of bronchiectasis, wherein the lower lobes are predominantly involved it is apparent that considerable difficulty may be encountered at times in differentiating such mucoid impaction from both pulmonary tuberculosis and bronchogenic carcinoma while planigrams have been suggested as a diagnostic aid it is pointed out that the large dilated bronchi remaining after evacuation might be mistaken for tuberculous cavities[449]

Pulmonary Microlithiasis This condition is characterized by the presence of innumerable calcified intra alveolar concretions or calcospherites throughout the lung particularly at the bases although little parenchymal involvement and few pulmonary symptoms are present in the early stages interstitial fibrosis pulmonary insufficiency, and cor pulmonale may ensue in the absence of a significant infectious or occupational background the cause is usually obscure, it may possibly be related to the presence of a peculiar type of hyperimmune pulmonary exudate the studies by Sosman and his colleagues on pulmonary alveolar microlithiasis are classic, it is of great interest that 13 of their 23 new cases occurred within five families overexposed or overpenetrated films are necessary to reveal the pathognomonic fine sand like particles of calcific density and uniform size that are uniformly spread throughout both lungs while there may be some accentuation of the lesions along the pleural surfaces, they are neither conglomerate nor coalescent[450]

Contusion of the Lung Pulmonary consolidations of varying extent not infrequently result from trauma to the chest with or without associated fractures of the ribs[455] these areas will usually resolve within several days, in this same regard pulmonary contusions with pneumatocele formation may be encountered the cavities being either unilocular or multi-

Hand Schuller Christian Disease See page 207
Pulmonary Venous Obstruction See page 130

Neoplasms

Bronchogenic Carcinoma Suspect and pursue this diagnosis in *all* cases of recurrent pneumonitis particularly in adult males who have been heavy smokers, it can masquerade as *any* type of pathologic pulmonary condition, even producing roentgenographically benign thin walled cavities, the Horner s syndrome, hypertrophic osteoarthropathy, polyneuritis, metastases to various organs, and the superior vena caval syndrome are but a few of the manners in which a lung malignancy may also first become manifest clinically, if two or more contiguous segments of the lung are involved by an obstructing bronchogenic carcinoma the lesion should usually be sufficiently proximal to be visualized by bronchoscopic examination (p 334) [451]

Pulmonary Metastases In general, miliary metastases turn out to be carcinomas whereas large nodules are usually sarcomas, hypernephromas, melanomas, or testicular tumors, solitary metastases may be present for years, in about 20 per cent of patients with metastases to the lung, the bronchus is involved suspect lymphangitic carcinomatosis in the presence of a progressively severe unexplained, and intractable asthma or cor pul monale (p 325), in contrast to the repeated episodes of pneumonitis in primary bronchogenic carcinoma pneumonitis is produced infrequently by pulmonary metastases unless significant bronchial obstruction is produced concomitantly

Pulmonary Adenomatosis Suspect this unusual malignancy when large amounts of clear mucoid sputum are associated with progressive con solidation fever and profound dyspnea, cytologic studies of the sputum will usually reveal the characteristic tall columnar cells [46] small foci of calcification have been noted in pulmonary adenomatosis—with or with out previous radiation—which histologically resemble the psammoma bodies observed in papillary tumors of the ovary and thyroid gland [46 c]

Bronchial Adenomas The less common cylindromatous type is more invasive than the carcinoid type the occasional presence of calcification may be quite misleading by x ray, both diagnostically and prognostically (p 346) [464, 1068, 1069]

Bronchial Papillomatosis The widespread involvement of the segmental bronchi that can follow the long standing presence of laryngeal papillomatosis is attended by the potential complication of severe recurrent pneumonitis, two other sequelae consist of massive hemoptysis and malignant degeneration it would appear that these tumors can arise both *in situ* within the bronchi and as transplants resulting from previous laryngeal surgery for the removal of the papillomas there [463]

Nontuberculous Pulmonary Cavities and Pseudocavities

In view of the wide variety of nontuberculous diseases or processes that can produce or simulate cavity formation within the lungs, and the almost

pulmonary edema, hypervolemia, and superimposed pulmonary infection[457]

The Syndrome of Intralobular Sequestration due to a Lower Accessory Pulmonary Artery This diagnosis should be considered in patients with recurrent lower lobe pneumonia, particularly when the posterior basal segment is so affected, or when a mass is associated with a finger like appendage extending to the aorta while the pulmonary mass is usually cystic and located in the posterior part of the lower lobe, instances of upper lobe sequestration are on record where the anomalous blood supply stemmed from the subclavian artery failure to anticipate these anomalous vessels could result in severe bleeding during thoracotomy[458]

Idiopathic Pulmonary Siderosis This unusual disorder may simulate a pneumonitis, multiple small pulmonary hemorrhages produce an inflammatory reaction and result in hemosiderin deposits

Endocarditis Refer to preceding portions in this chapter for a discussion of the pulmonary complications of this condition, particularly when due to a right sided endocarditis (p 117)

Pulmonary Venous Obstruction Andrews has pointed out that obstruction to the outflow of a pulmonary vein can result in a severe form of interstitial fibrosis in the lung parenchyma drained by the obstructed vein in five cases of this unusual form of interstitial fibrosis, the obstruction proved to be variously due to a large intracardiac myxoma, a large auricular thrombus, mediastinal collagenosis and congenital stenosis of the pulmonary veins[460b]

Interatrial Septal Defect In the patient who is forty five years or older and who exhibits a prominent systolic murmur over the base of the heart along with recurrent respiratory infections, the possibility of an interatrial septal defect must not be discounted solely on the basis of the age factor

Interstitial Pulmonary Fibrosis

The Hamman-Rich Syndrome Suspect this diagnosis in the presence of progressive pulmonary infiltration that is accompanied by severe dyspnea orthopnea and cyanosis, cor pulmonale secondary polycythemia, and clubbing of the digits frequently occur, these features result from the interference with the exchange of gases due to the marked generalized thickening of the alveolar walls[459] do not confuse this entity with pneumomediastinum, characterized by Hamman s sign—i e a to and fro crunching clicking, or tapping sound heard over the precordium, the author and others have observed patients with the Hamman Rich syndrome who survived up to seven years[459]

Complications of Antihypertensive Therapy A progressive and severe type of interstitial fibrosis has followed the prolonged administration of potent antihypertensive drugs most notably hexamethonium given with or without hydralazine,[460a] these patients are found to have a fibrinous pneumonitis resembling that of the so-called ' uremic pneumonia ' even though azotemia is frequently not present, extreme tachypnea is the most impressive clinical manifestation

such cases but which receive little emphasis in the training of most physicians will be cited in the following résumé and in Section VIII of Part II (Studies of the Central Nervous System)

One must be cognizant of the significant change in the clinical course of patients with a *brain abscess* since the use of the antibiotics In their review of 99 cases of surgically or pathologically verified brain abscesses, Loeser and Scheinberg noted the following evolving features (1) there are more patients now encountered in the older age groups (2) in one out of four cases the brain abscess was not accompanied by evidence of any previous infection, (3) while there has not been a significant change in the distribution of the sites of brain ab cesses since the introduction of the antibiotics one fourth of these patients are found to have sterile abscesses (4) the *Streptococcus viridans* organism is found with greater frequency now than the *Pneumococcus* (5) the temperature and pulse are often of little value in indicating the presence of a suppurative process—the white blood count, the spinal fluid studies and the x ray studies of the skull being of some added help, but not in more than one half of the cases, and (6) once neurologic manifestations develop the course tends to progress rapidly downhill [455b]

The finding of a spontaneous nystagmus in the patient with a purulent otitis media could prove to be of considerable importance in pointing to the possibility of impending intracranial suppuration When the nystagmus is detected in the vertical direction it may be indicative of a lesion in the rostral or pontine brain stem or of a temporal lobe abscess that is rupturing into the lateral ventricle *

A focal embolic encephalitis rather than abscess formation is more prone to occur in *endocarditis*

The *brain abscess associated with bronchiectasis* is usually due to the local centripedal extension from a concomitant sinusitis particularly in the case of the frontal sinuses, rather than to metastatic infection

The occurrence of a "*paradoxical cerebral abscess* in the pre ence of congenital heart disease, but without bacterial endocarditis merits some attention A number of cases demonstrating this combination have been reported [472] The majority of these abscesses are solitary and therefore potentially amenable to surgical cure (It is postulated that with the recirculation of the venous blood through the systemic circulation organisms of a transient bacteremia might not be completely filtered out by the pulmonary capillaries)

It is imperative that a *subdural abscess or empyema* be recognized as soon as possible in view of its acute fulminating nature [466 468] The clinical course and prognosis differ from that of most cerebral abscesses This infection most often complicates a frontal sinusitis or otitis, the symptoms of which (pain swelling discharge) are usually exacerbated Meningeal signs, Jacksonian seizures focal neurologic signs and a hemiparesis or hemiplegia then ensue The drainage from a subdural empyema that can be achieved by multiple burr holes is usually quite unsatisfactory Experience has demonstrated the frequent necessity for wide craniectomy and

* See reference 385 in Part II

reflex association of cavitary disease with pulmonary tuberculosis, it behooves the medical consultant to be cognizant of the many clinical bacteriologic and radiographic pitfalls involved This applies even when the abnormalities in the chest films appear to be supported by the finding of acid fast organisms in the sputum Only such vigilance can insure that the patient will not be deprived of specific nontuberculous therapeutic measures or subjected to undue procrastination Detailed bacteriologic study is necessary to rule out the presence of the chromogenic acid fast bacilli (p 153)[547, 548] It is also pointed out that there is considerable hazard in diagnosing closed negative cavity healing by laminographic examination[546b]

Reference is made throughout this text under the infectious diseases (the bacterial, viral, and rickettsial pneumonias and lung abscesses, the fungus and yeast infections the parasitic diseases) sarcoidosis (p 204), pulmonary infarction (p 212)[454b] pulmonary contusion (p 128) the dyscollagenoses (pp 303–309) Wegener's granulomatosis (p 206)[451] pulmonary neoplasms (p 334) anthrasilicosis (p 126)[444a] radiation pneumonitis (p 398) and the Loffler syndrome (p 64) to the possible occurrence of pulmonary cavitation in these disorders The coexistence of tuberculosis and either another bacterial infection a fungus disease or a neoplasm will also receive attention (p 351)[535, 537] The reader is also referred to the fine review by Laforet and Laforet on this subject[485]

Several relevant comments are in order Apparent cavitation is not infrequently observed during the resolution of lobar pneumonia primary atypical (virus) pneumonia and suppurative bronchopneumonia (especially in children) Subsequent radiographic follow up in these patients will usually clarify the issue Bronchographic examination may point out the nature of the cavity in a stable bronchiectatic process The large dilated bronchi in mucoid impaction of the bronchi that remain after their evacuation might suggest cavities[449] Cavitation is far more prone to take place in the presence of pulmonary malignancy (bronchogenic carcinoma squamous-cell carcinoma adenocarcinoma metastatic disease lymphoma) than when benign pulmonary tumors are present This results from the development of central necrosis in a rapidly growing tumor which has either outstripped or mechanically interfered with its blood supply[436] The author has encountered several instances where cavities with such thin walls were present that the attending radiologists and clinicians alike did not believe an underlying neoplasm could be present

Finally one must constantly be on the alert for both artifacts and extrapulmonary disorders that might simulate pulmonary rarefaction These entities include hiatal hernia loculated pneumothorax encapsulated empyema and anomalies of the costal cartilages (particularly the first one) or the chest wall (such as congenital unilateral absence of the pectoral muscle, p 389)[1154]

MENINGITIS AND MENINGISMUS OF OBSCURE ETIOLOGY

A comprehensive discussion of the causes of meningitis and meningismus can be found in most standard medical textbooks A number of important considerations which frequently arise in the clinical analysis of

anterior flexion of the head onto the chest, and the head drop (i e, the backward arching of the head as the body is raised from the supine position by the placement of the examiner s hands behind the patient's shoulders)

There are a number of *poliomyelitis like diseases* which are now being diagnosed more often This increasing recognition is attributed to (1) the improbability of poliomyelitis as shown by the subsequent course of the patient, (2) the increasing resistance being produced in the general population against poliomyelitis by active immunization, and (3) the exclusion of other viral etiologies by negative serologic studies of the spinal fluid and the serum In this regard, reference is made to *epidemic neuromyasthenia* (also known as "Iceland disease' and "benign myalgic encephalomyelitis)

In detailed studies of over 200 patients with epidemic neuromyasthenia by two groups of epidemiologists a prodromal period characterized by minor systemic complaints was noted[477] The full blown clinical picture that ensued consisted of localized muscular weakness, myalgia, headache, stiffness of the neck and back gastrointestinal symptoms (nausea, vomit ing diarrhea) and a low grade fever Neither muscular atrophy nor lasting muscular flaccidity are characteristic of epidemic neuromyasthenia, how ever Many of these patients also exhibited unusual fatigability diplopia menstrual disturbances, alterations in their emotional status and mentation cutaneous sensory disturbances (including chest pain and abdominal pain) and vasomotor instability with angiospasm Patients with the non-paretic form of the disease have shown all variations of these symptom complexes One patient that the author has personally encountered ex hibited such severe muscular sensitivity that he remained in opisthotonus for over two days which could be relieved only by intravenous Amytal

Four remarkable features of this disorder are (1) the protracted sub-acute course (usually over six months) (2) the high incidence of remissions and exacerbations which could be induced by exertion, the menses, and coldness or dampness, (3) the paucity of positive laboratory findings fol lowing intensive bacteriologic cytologic, and serologic study of the spinal fluid, the blood the throat, and the stools and (4) the predominance of young and middle-aged female patients in the several series reported

The possibility of *tick paralysis* might be entertained in unusual para lytic situations that resemble poliomyelitis, especially in females whose long hair might conceal the tick[474] This differentiation assumes even greater significance when it is realized that the disease may be cured promptly if detected in time and that the greatest incidence of this disorder during the summer months coincides with that of the poliomyelitis season Patients so infested can also demonstrate a rapidly ascending paralysis sug gestive of the Guillain Barré syndrome In his review of the subject, Costa has set forth the manner by which the tick should be removed but points out the readiness with which the engorged tick can be mistaken for a pedunculated fibroma or a wart[474]

'*Benign aseptic meningitis* may be due to many infections, most notably lymphocytic choriomeningitis mumps, herpes simplex leptospirosis infectious mononucleosis, lymphogranuloma venereum the Coxsackie

open drainage, combined with intensive antibiotic therapy, if one is to obtain adequate decompression and drainage[468c]

Collections of subdural fluid with a high protein content have also been reported with increasing incidence following *Hemophilus influenzae* meningitis in infancy[46] • Unless the subdural space is drained and irrigated with dilute solutions of antibiotics, it might prove fatal within two weeks (Resorption of the exudate may occur with needle aspiration alone, however) It is possible that the relatively high incidence of the neurologic "survival syndrome" due to *postmeningitic subdural effusions* in infants and children may be induced by the withdrawal of excessive amounts of fluid at the time of diagnostic spinal taps[467b] This diagnosis can be readily established by the performance of bilateral subdural taps through the open fontanel in any child whose clinical response to antibiotic therapy is poor Consequently, it appears wise to limit the diagnostic spinal puncture to a single tap in infants and children with bacterial meningitis, during which not more than 3 ml of fluid are removed

A suppurative *longitudinal sinus thrombophlebitis* should be considered when convulsions that occur alternately on both sides, marked papilledema, and an aphasia or hemiplegia follow a frontal sinusitis, an otitis media, or infection of the face With the same etiologic background, a temporal headache, papilledema and evidences of sepsis should suggest a *lateral sinus thrombosis* Similarly the occurrence of headache, facial pain, eyelid edema, proptosis and an oculomotor palsy indicate a *cavernous sinus thrombosis* Profuse epistaxis with meningitis or meningismus should suggest a *thrombosis of the ethmoid veins or of the cavernous sinus*[469, 1038]

The cutaneous manifestations of cavernous sinus thrombosis are depicted in Figure 66 (Atlas page 41)

A communication of the subarachnoid space with a *congenital dermal sinus* should be suspected when unusual organisms are found in either a meningitis or abscesses of the brain and spinal cord This consideration is especially pertinent in patients below the age of five years The sinus may appear as an insignificant dimple located at any point from the occiput to the coccyx[470]

In the presence of acute diffuse root pain and spinal cord dysfunction, the diagnosis of a *staphylococcal epidural abscess* resulting from a skin infection or a vertebral osteomyelitis must receive prompt attention[471] The finding of a spinal block or changes in the spinal fluid characteristic of epidural sepsis will avert the usual misdiagnoses of leptomeningitis, poliomyelitis, or infectious polyneuritis Once the diagnosis is made laminectomy for drainage of the epidural space becomes a true surgical emergency See the discussion under Group XII (p 378)

The diagnosis of *poliomyelitis* should be made with great caution in the presence of either symptomatic anesthesia or a spinal fluid lymphocyte count exceeding 500 cells per ml "Poliophobia" and lymphocytic choriomeningitis, respectively are more likely under these instances Similarly, a symmetrical paralysis, convulsions and coma are infrequent in this disease Considerable care should be taken in differentiating true paralysis from the pseudoparalysis that may be associated with scurvy, fractures osteomyelitis perinephric abscess and hysteria[474] Two signs of considerable aid in the diagnosis of poliomyelitis consist of the nuchal rigidity to

that such terminology be carefully worded Adams and Weinstein, and Webster could find no verified cases of acute encephalitis lethargica, St Louis encephalitis, or eastern equine encephalitis in the New England states from 1939 to 1955[478] In 1955, however, 4 cases of eastern equine encephalitis in humans were encountered[478b] c A similar review of the literature during this period revealed only 18 cases of equine encephalomyelitis from the entire United States Nevertheless, these disorders must be borne in mind in areas where fatal encephalomyelitis in horses is endemic, and even more so when the potential for exposure is constant, as in the case of farmers If this diagnosis is suspected, acute phase and convalescent phase serum for neutralization and complement fixation studies, or post mortem brain (within five days after the onset of the encephalitis) for animal inoculation studies are imperative

A fulminating meningitis is prone to complicate the *dural tears associated with fractures* of the paranasal air sinuses the middle ear, and the mastoid air cells[479] Pneumocephalus and cerebrospinal fluid rhinorrhea or otorrhea are clues to this diagnosis (In the absence of mixing with serum or blood from a recent injury, the analysis of its sugar content can confirm the presence of cerebrospinal fluid) It is necessary to close the fistula between the intracranial cavity and the nasopharynx in instances of chronic and delayed traumatic cerebrospinal rhinorrhea in order to prevent further bouts of meningitis, cerebritis, and brain abscess

An acute disseminated encephalomyelitis occasionally occurs before the rash becomes apparent in measles chickenpox, and a number of other *exanthematous diseases* It may be so mild, however, as to go undetected until behavioral abnormalities appear years later

A "serous meningitis ' which is benign and generally unresponsive to antibiotics occurs in *scarlet fever*

Careful inquiry into contact with a possibly rabid dog three to eight weeks previously must be made in patients exhibiting unexplained acute restlessness irritability and excitement, alternating with drowsiness In a recent report of three cases of *rabies* the diagnosis had not been made or even clinically considered once[480] One must always entertain the possibility of human to human transmission of rabies and administer prophylactic rabies therapy to anyone who has been contaminated by an individual with furious human rabies[480b]

In the presence of increased intracranial pressure a lymphocytic or mononuclear cell pleocytosis a reduced spinal fluid sugar and no response to antibiotic therapy, the diagnoses of *meningeal gliomatosis metastatic sarcomatosis, and meningeal meningiomatosis* merit consideration[481] As these descriptions indicate the meninges can be diffusely involved from underlying gliomas medulloblastomas, ependymomas and other types of neoplasms Tumors may also originate primarily from the meningothelial cells and fibroblasts of the meninges

In the patient with *acute leukemia* who develops meningeal signs and who remains afebrile and free of spinal fluid changes the probability of a leukemic meningitis ' is quite likely[48]

A number of reports have shown the unusual ability of *Pseudomonas aeruginosa* (or *Bacillus pyocyaneus*) to invade the meninges *following spinal*

group of viruses, and herpes zoster[473] This diagnosis should be made *only* in the absence of organisms from the spinal fluid, in the absence of local parameningeal infection or general disease, and in the absence of a local endemic or epidemic It must be appreciated that these infections are not always "benign" clinically, as witnessed, for example, by the severe or fatal encephalitis and transverse myelitis that has complicated lymphocytic choriomeningitis[473f] and fatal mumps meningoencephalitis[58se] Very low spinal fluid sugar levels may occur in the last two diseases

With the rapid progress in virology, one can anticipate the isolation and identification of increasing numbers of specific viruses from patients with lymphocytic or aseptic meningitis For example there is little doubt now that both ECHO viruses Type 6 and Type 9 were probably the cause of several such epidemics (some associated with a morbilliform eruption) and that the Group A Coxsackie viruses might even be isolated from patients with proved paralytic poliomyelitis (p 741)[473b, e] There are occasional instances in which an aseptic meningitis has followed an unusually chronic but eventually benign course In most of these cases it is difficult to establish a definitive bacterial, luetic, or viral etiology[473e]

The possibility of *meningovascular syphilis* should always be considered in the presence of atypical central nervous system disorders and meningeal manifestations This is a particularly important consideration when Negroes are so affected regardless of age

There is a significant incidence of simultaneous double infection in purulent meningitis affecting small children In one series of 10 such cases the *Hemophilus influenzae* organism occurred in 9 cases and was associated with either the meningococcus the streptococcus, the pneumococcus, or *Escherichia coli*[475]

Tuberculous meningitis can exhibit a large percentage of polymorphonuclear leukocytes in the spinal fluid early in its course The low spinal fluid sugar and chloride levels are most helpful and may avert an erroneous diagnosis This disease should be borne in mind when meningeal signs occur in postpartum women (especially when they have had spinal anesthesia) because of the well recognized tendency for hematogenous dissemination to occur following delivery (p 149)[63a]

Consideration should be given to the various causes of *polyneuropathy* enumerated under Group XII when an acellular fluid is encountered in the presence of meningeal and neurologic signs (p 379) Diphtheria, trichinosis, drug or serum reactions and poisonings merit particular attention in this regard

The course of a number of systemic diseases most notably *sickle cell anemia porphyria*, and *lupus erythematosus* may be punctuated by acute crises that simulate meningitis

Torulosis produces a chronic lymphocytic meningitis which should not be mistaken for that due to tuberculosis The significance of this infection in the lymphomas is stressed elsewhere (p 167) The *Cryptococcus neoformans* organisms should not be confused with red cells or lymphocytes Double infections in the spinal fluid have been encountered in these cases particularly with *Escherichia coli*[809b]

The diagnosis of a *primary viral encephalomyelitis* must be made with the greatest caution in nonendemic areas Moreover, it is most important

influence of antibiotic therapy is not limited to moniliasis and mucormycosis For example, a "bloody" red sputum that may simulate hemoptysis can be produced in the patient with chronic lung disease by the overgrowth of *Serratia marcescens* (*Bacillus prodigiosus*), an organism that contains a red pigment[48] A distinction should be made on the one hand between the surface proliferation of certain fungi (as with monilia and aspergillus) resulting from antibiotic therapy, and actual systemic and tissue invasiveness on the other The latter sequence tends to be most commonly associated with combined steroid and antibiotic therapy[511]

Several independent groups of investigators have clearly shown the frequent emergence of resistant *Micrococcus pyogenes* var *aureus*, *Escherichia coli*, paracolon bacilli, and various strains of *Proteus* over two to five year periods[489] Infection with these organisms is most likely to occur in the hospital environment ('nosocomial' infections) particularly following diagnostic or therapeutic instrumentation and operation on the urinary passages (One must constantly bear in mind the fact that it is usually the resistant *infection* rather than the resistant organisms which is of basic importance) In this regard, most observers have come to the conclusion that the sensitivity of bacteria to the antibiotics can be best determined by the tube dilution method rather than by the disc method which is likely to give misleading results (p 752)

Resistance of microorganisms to the antibiotics can develop in one of two basic manners i e within the individual patient and within the hospital population How the staphylococcus—which is so readily destroyed by moderate heat and by many antiseptics—and other organisms can cause so much damage in hospitals that are maintained as clean as possible is an enigma It may be that these organisms are capable of surviving and maintaining their virulence in fine dry dust over long periods of time They further exhibit remarkable ability for widespread dissemination and penetration, particularly as a result of dry dusting, dry sweeping floor polishing, and via the washing and toilet facilities used by patients and physicians It has also been found that blankets mattresses sheets, pillows urinals, and pajamas can serve as heavily contaminated reservoirs of the staphylococcus[490b c]

Jawetz has pointed out that the main problem in the hospital environment is currently focused upon the incidence of *antibiotic resistant staphylococci*, chiefly as they affect the following four groups of patients newborn infants mothers who are nursing infected newborn infants[551] surgical patients and individuals infected by the spread of these germs from surgical patients or as a result of inadequate isolation procedures[490a] Perhaps the most common site for the development of lesions due to contamination by resistant organisms is the skin particularly in the form of boils on the backs of patients who are confined to bed[490b] The following are recommendations for the control and the prevention of such hospital infections

1 Antibiotic prophylaxis should not be used indiscriminately in the majority of 'clean elective surgical procedures

2 An attempt should be made to "aim the potent antibiotic agents against specific organisms and *in full dosage*

anesthesia [483] A hemorrhagic meningitis may result from the thrombogenic and proteolytic actions of this organism (as is also the case in anthrax) Of 41 cases of *Pseudomonas* meningitis collected by Stanley, 14 followed diagnostic lumbar punctures, 13 resulted from traumatic penetration of the meninges, 10 complicated spinal anesthesia, and two followed pneumoencephalographic examination [484] Septic meningitis due to the streptococcus and to other organisms has also been reported [485]

INFECTIOUS COMPLICATIONS OF ANTIBIOTIC THERAPY

The unique infectious complications of antibiotic therapy are currently an important consideration in the general subject of infection [486 488] The problems associated with antibiotic resistant strains of pathogenic organisms (disruption of the normal ecologic balance with alterations of the intestinal bacterial flora, superinfection by bacteria yeasts and moldlike fungi and interference with normal antibody formation) should all be considered when patients receiving these agents demonstrate unexplained morbidity or relapse Actual antibiotic antagonism on the clinical level is probably quite uncommon, and paradoxically appears to be encountered most often when one is dealing with organisms that are quite sensitive to the several agents employed Several other potential complications of therapy with the broad spectrum antibiotics that are cited elsewhere include the development of pellagra (p 43), the interference with the evaluation of obstructive versus nonobstructive jaundice (p 88), and symptomatic bleeding due to the induced vitamin K deficiency (p 43)

Most physicians find it somewhat difficult to accept the increasing number of reports from ' the ivory towers that the prophylactic administration of the antibiotics either to comatose patients with no evidence of infection or to patients with "respiratory" poliomyelitis can cause more complications than if no such measures are employed Yet careful studies tend to point out that these agents do *not* prevent or ameliorate the infection resulting from indwelling catheters and that the incidence of pneumonitis and superinfection with gram negative rods or micrococci is actually increased [485b e]

We have only begun to understand the immense complexity of the normal symbiotic intestinal flora, comprising as it does numerous bacteria (among which are the coliforms, *Klebsiella Proteus, Shigella, Pseudomonas Salmonella* gram negative enterobacteriaceae, *Bacteroides, Streptococcus Staphylococcus, Lactobacillus* and *Clostridium*) and divers fungi, yeasts, protozoa, viruses and phages The changes that are effected either by the entrance of a pathogen into this biologic maze or by the administration of antibiotics (especially on a protracted basis) are certainly far from clear For example, it has been shown that many coliform bacilli normally exert a significant antibacterial action against the salmonellae the shigellae, and even the pathogenic coliform organisms Accordingly, such protection against certain enteric pathogens (especially the salmonellae) may be lost as a result of the elimination or inhibition of the coliform bacilli by potent antibiotics [487b 89 a]

The overgrowth of pathogenic and nonpathogenic molds under the

tion This can be obviated to a large extent by the use of intermittent courses of treatment [497]

SYSTEMIC CONDITIONS PREDISPOSING TO REPEATED SEVERE INFECTION

In concluding the general subject of infection the reader is reminded of several systemic illnesses predisposing to repeated severe infection which in themselves are frequently very subtle and otherwise asymptomatic at the time An attempt will be made to indicate the mechanisms and basic nature of this underlying susceptibility to infection It is apparent however, that this still remains fertile soil for investigation, as exemplified by the great current interest in properdin and the various globulins

The potential factors influencing the susceptibility to any one disease may be numerous [498] This consideration is rather well exemplified in the case of poliomyelitis For example pregnant women are much more susceptible to the disease—more so in the case of multiparous than primiparous individuals and more so during the second trimester of pregnancy There seems to be a definitely greater incidence of this disease around the menstrual period The incidence of bulbar poliomyelitis is three times greater when the tonsils are absent Finally the older age groups are much more prone to exhibit general bladder and respiratory paralysis than patients in the earlier decades

Specific races are definitely predisposed to a more virulent and disseminated type of certain infectious diseases This diathesis is shown most strikingly in the case of tuberculosis (Negroes Indians Chinese) (p 149), and coccidioidomycosis (the dark skinned races) (p 166)

The propensity with which patients having *diabetes mellitus*, known or unsuspected are subject to infections of a pyogenic nature is universally appreciated [499] Unfortunately it is altogether too common for this type of patient to have gone through repeated bouts of skin, respiratory or renal sepsis—promptly responding on each occasion to the antibiotics—before the urine or blood are tested for sugar There have been many explanations set forth to explain the susceptibility of patients with diabetes to infection among which are protein depletion tissue hypoxia inhibited lactic acid hypokalemia and the presence of increased amounts of glycerol in the case of the tubercle bacillus The presence of a neuropathy in patients with long standing diabetes often accounts for the long delay in their recognizing the onset of a pelvic or urinary tract infection Although infection with the ubiquitous mucorales is unusual diabetes apparently specifically predisposes to fatal invasion by this fungus In fact signs of retro-orbital infection (usually unilateral) subsequent ophthalmoplegia and meningoencephalitis in a diabetic should suggest the possibility of cerebral mucormycosis [500]

Reference was previously made to the frequency with which superficial moniliasis complicates juvenile *hypoparathyroidism* [L] Many mycotic infections in their disseminated form are reported as complications of *Boeck s sarcoid* including histoplasmosis coccidioidomycosis cryptococ

3 The use of certain antibiotics should be eliminated in hospitals by common consent of the staff members, except in the management of specific patients This applies in particular to the newly introduced antibiotics such as novobiocin

4 Meticulous asepsis and antisepsis must again become the order of the day if cross contamination is to be minimized The chief offenders in this regard are unfortunately very frequently the senior surgeons and physicians

5 Identification of staphylococcal infections in infants (who are remarkably favorable culture media for this organism) and their mothers should be made as soon as possible (p 153)

6 Considerable skepticism should be harbored for any claims relating to the 'synergistic' activity of antibiotic combinations, except in well defined circumstances This particular theme will be further amplified under the chapter on 'Iatrogenic Illness' (p 407)

The increasing practice of preserving meat fish and other foods with the antibiotics may serve to further compound the incidence of antibiotic resistant organisms For example it has been clearly demonstrated that mice which are fed a prolonged diet of streptomycin treated food develop a resistance to the drug within one month that is five times greater than that normally expected

Particular note is made of the distressing and increasing problems of infection by antibiotic resistant staphylococci[491] (p 153) and the entity of *pseudomembranous enterocolitis* [49] Although the latter condition was encountered prior to the antibiotic era and is still occasionally observed in the absence of antibiotic therapy [493] it is distinctly more frequent now This condition should be borne in mind when patients with recent abdominal surgery (including cesarian sections and abruptio placentae) exhibit unexplained toxicity and shock [494] [495] The severe diarrhea is akin to that observed in staphylococcal food poisoning and can be attributed in large measure to the production of a potent enterotoxin Pseudomembranous changes have also been found in the tracheobronchial tree and in the pancreas in association with infection due to antibiotic resistant organisms [495a]

When considering this disorder in an elderly patient with the clinical picture of severe progressive upper gastrointestinal illness and concomitant sepsis one might also contemplate the possibility of an *acute phlegmonous gastritis* [496] This fulminating infection may be hematogenous or it may be initiated by trauma to the stomach from food poisoning, a gastric ulcer, or an ulcerating carcinoma from which bacteria can spread to the submucosal tissues

It is equally vital to appreciate the fact that relapse is apt to occur if specific antibiotic therapy is administered early in the course of certain infections before sufficient antigenic stimulation and immunity have developed Such exacerbations are particularly prone to ensue in the infections due to the intracellular organisms or parasites most notably the rickettsioses typhoid fever tularemia and brucellosis The same consideration applies when the antibiotics are administered continually in these disorders since such regimens might prevent adequate antigenic stimula

spontaneously), and (4) the fact that both vaccinia and varicella may assume a disseminated and fatal character when they affect patients receiving cortisone[510] Severe moniliasis involving the oral cavity, pharynx lungs intestinal tract, skin and vagina has been observed following adrenal steroid therapy for certain debilitating diseases, particularly the malignant hemopathies Some authors have indicated that thrush septicemias might even occur in such instances resulting in a monilial endocarditis, meningitis and metastatic abscesses A similar situation may also exist when the *antimitotic drugs* (aminopterin 6-mercaptopurine) are employed[500, 511, 51] It is not unlikely that these complications result from an interference with the reactivity of the antibody producing sites to the antigenic stimulus by the steroids, rather than there being an accelerated antibody destruction[513]

A somewhat related consideration pertains to the recrudescence of clinical infection that is observed in a number of diseases in which the basic infection was quiescent until reawakened by some *stress* mechanism The stimulus is usually either surgical trauma or a superimposed infection This phenomenon has been most commonly encountered in typhus the other rickettsioses, typhoid fever, brucellosis, herpes simplex and malaria[497]

A number of *hematopoietic disorders* predispose to infection Ulceronecrotic lesions of the oral cavity pulmonary infection and perirectal sepsis are frequently the presenting complaints in patients with *monocytic leukemia*[514, 515] A disseminated and hemorrhagic form of herpes zoster is observed on a number of occasions as a complication of *chronic lymphatic leukemia* (p 181)[516] The febrile episodes which so frequently punctuate the course of the patient with leukemia are probably the result of transient bacteremias usually with staphylococci *Pseudomonas* or the colon bacili[657c, d] There is a very high susceptibility to staphylococcemia among patients with acute leukemia

An illustration of symptomatic herpes zoster appears in Figure 18 (Atlas page 11) The oral manifestations of monocytic leukemia are depicted *in Figure 29 (Atlas page 19)*

In several chapters of this book the diagnostician is reminded to seek out an underlying *lymphoma* leukemia or myeloma when torulosis (cryptococcosis) is encountered (pp 167 and 182) The diathesis that patients with Hodgkin's disease harbor for the development of tuberculosis will be discussed at further length in a subsequent section (p 182) An occasional striking feature of *myeloma* is the recurrence of pneumococcal infections (pneumonia meningitis pyarthrosis) and bouts of sepsis due to other organisms[517] This is probably a result of the defect in gamma globulin primarily due to the diversion of gamma globulin precursors for the synthesis of the abnormal component[518] Lawson and his colleagues have repeatedly demonstrated not only the absence of multiple specific bacterial antibodies in the course of myeloma but also a progressive loss of isoagglutinins and amboceptor as the illness progressed[519]

More evidence of the poverty of the immunologic mechanism in adult patients with neoplastic disease of the hemopoietic and reticulohistocytic systems is the unusual terminal complication of such disorders by *cytomegalic inclusion disease*[660] In the majority of the patients described with this infection the malignant lymphoma or leukemia was attended by

cosis, and blastomycosis[747] There is also an unusual susceptibility to infection in patients with primary and secondary *amyloidosis*[198]

The general depletion in *chronic alcoholism and cirrhosis* predisposes to a number of infectious complications, frequently without the expected white blood cell response Postpneumococcal empyema, peritonitis, mycotic invasion, and infection due to the Friedlander's bacillus are not uncommon in such debilitated individuals Furthermore, severe liver disease predisposes to bacteremias by the gram negative bacilli This may variously be the result of the impaired filtering action by the hepatic reticuloendothelium the portalhepatic venous shunting of organisms coming from the intestine and various immunologic defects[501] The importance of good nutrition to the organism's resistance to infection is pointed out by the enhanced susceptibility of animals to infectious disease within 36 to 48 hours after the withdrawal of food[502]

The predisposition to fatal intercurrent infections in *lipoid nephrosis and the nephrotic syndrome* especially by pneumococcal or streptococcal peritonitis septicemia, and pneumonia was frequently apparent before the availability of the antibiotics[503] This phenomenon may be attributed in part to the marked reduction, aberrations or absence of normal gamma globulin[504] The infectious diathesis in these disorders is not limited to children or to the aforementioned organisms This is evidenced for example, by the occurrence of influenzal meningitis in adults[505] (The clinician must bear in mind that nephrotic crises occur which may simulate a peritonitis or a surgical emergency)[506] It has been shown experimentally however that acute renal failure *per se* does not interfere with the capacity of the organism to resist a number of infections[507]

The development of fatal and at times unrecognized disseminated sepsis in association with the administration of *cortisone* or its analogs was previously cited (p 15)[21] The hematogenous dissemination of tuberculosis and other infections (especially streptococcal and antibiotic resistant staphylococcal sepsis) during therapeutic hypercortisonism is well appreciated but necessitates continuous re-emphasis in patients receiving these hormones[508] [509c] When a possible infectious complication of steroid therapy is being considered, it is well to bear in mind that the adrenocortical hormones exert very little effect either quantitatively or qualitatively, on a positive tuberculin test Both the steroids and the antibiotics have been known to provoke or to activate a generalized or focal salmonellosis[59a]

The above issue is all the more important if the steroids are administered for a disease such as *systemic lupus erythematosus* in which the patient's resistance to infection is already lowered[509] A salmonella osteomyelitis of the vertebral bodies causing destruction of the joint space and the development of a paravertebral mass has also been encountered as a complication of disseminated lupus erythematosus[510a]

That these considerations concerning the infectious complications of steroid therapy apply to infection by organisms other than the bacteria is underscored by the following observations (1) the development of pulmonary or cerebral mucormycosis especially in the presence of leukemia and myeloma[512] (2) the spread of the systemic mycoses following steroid therapy in patients who were misdiagnosed as having sarcoidosis (3) the severity of herpes zoster, even in children (where the disease rarely occurs

Hypogammaglobulinemia

Hypogammaglobulinemia and *agammaglobulinemia* in both children and adults have now been described in a sufficient number of patients to merit serious consideration of these disorders in situations of "immunogenic paralysis"[5, 5] The gamma globulin is very low and the beta 2 globulin is also diminished In contrast to normal concentrations of gamma globulin (determined immunochemically) of from 1100 to 2100 mg per 100 ml, levels of from 0 to 30 mg have been encountered in the congenital cases, and from 0 to 76 mg in the acquired cases[5, 5e] The flocculation tests often remain negative, even in the presence of significant liver damage There is a total absence of circulating and fixed antibodies (both inherited and acquired) before and after an antigenic challenge

Congenital agammaglobulinemia (also known as the 'antibody-deficient syndrome') primarily affects males and is further characterized by their inability to make plasma cells Inasmuch as the life span of injected gamma globulin in these patients is virtually the same as that in normal individuals the basic defect would appear to be failure to synthesize gamma globulin rather than an excessively rapid destruction or loss of this protein Not only is it known that the deficiency of gamma globulin is often incomplete but also that at least two plasma proteins (which migrate as beta globulins)—in addition to the gamma globulin—are absent or deficient in this condition[5, 9b] Furthermore it has been pointed out by Gross that these children respond similarly to various sensitizing chemicals and hybrid bacterial protein allergens so that some additional cellular immunological mechanism is also undoubtedly involved in agammaglobulinemia

A specific diagnostic test with horse antihuman gamma globulin serum and a specific therapy in the form of gamma globulin are available for this disorder (p 751) One can use the standard Coombs serum to which Coombs positive red blood cells are added to ascertain the presence of hypogammaglobulinemia The ab ence of erum isohemagglutinins in patients of blood groups O A or B may also serve as a simple, rapid, and economic preliminary screening test for this condition The correlation between the relatively low titers of serum isoagglutinins and the low levels of gamma globulin as determined electrophoretically and immunologically is only of a rough nature however[5, 26]

Hypogammaglobulinemia hould therefore be suspected under the following circumstances (1) a history indicating a grossly inadequate resistance to infection (2) failure to develop clinical immunity or the expected laboratory evidence of antibody production (negative tuberculin tests positive Schick and Dick tests second attacks of rubella and mumps) after adequate previous antigenic stimulation (3) an unexpectedly normal result with a laboratory test that depends upon abnormalities in the serum gamma globulin (thymol turbidity cephalin flocculation) and (4) the aforementioned absence of serum isohemagglutinins The dermatologic manifestations of hypogammaglobulinemia include recurrent pyodermas, furunculosis cellulitis generalized postvaccination vaccinia extensive

marrow failure and a panhematocytopenia, and with extensive neoplastic replacement of the lymph nodes and spleen

This infection is due to the "salivary gland virus" (actually a group of species specific sialadenotropic viruses) which ordinarily evokes little tissue response It is more commonly noted in the salivary glands of new born infants dying of unrelated conditions In its disseminated form among adults the most striking pathologic change consists of a florid lymphocytic inflammatory response in the tissues a fibrinous pneumonia with miliary necrosis and a multifocal necrosis of the adrenals The diagnosis is first suspected by the pathologist because of the characteristic gigantism of the parasitized cells which contain large intranuclear inclusion bodies (In the past these cells have undoubtedly been confused with neoplastic reticulohistiocytes or hemocytoblasts with large nucleoli) (Also see p 170)

Another hematologic disorder that appears to predispose to bacterial invasion particularly in the form of a salmonella osteomyelitis, is *sickle cell anemia*[715d] *The disseminated reticuloendothelioses* are at times characterized by recurring secondary infections, especially in the Letterer Siwe disease

Recurrent infection is often the presenting symptom of a *chronic neutropenia* particularly in the presence of *hypersplenism* The latter may be due to hyperplasia, portal hypertension lipid cellular disorders, or benign and malignant splenic tumors[520] *Radiation injury* from various sources must not be overlooked in the presence of unexplained leukopenia An interesting association of *cyclic agranulocytosis* and infection is occasionally noted with the menstrual cycles[6, 18] *Congenital granulocytopenia* occurs in both sexes and is usually initially manifested by recurrent furunculosis

Smith and his colleagues have demonstrated the striking incidence of subsequent severe infection and sepsis in 19 patients who were subjected to a *splenectomy* six terminating fatally[6] The infections primarily encountered in this unique group included meningitis (usually pneumococcal) acute benign pericarditis (in patients with Cooley s anemia) acute endocarditis and other forms of sepsis It is of interest that no diminution in the concentration of gamma globulin could be found in these patients This complication is most noteworthy in young children and usually occurs within two years following the surgical procedure Similarly there is apt to be a marked susceptibility to infection in adults following splenectomy in the presence of myeloid metaplasia (p 203)[729] The autosplenectomy of patients with sickle cell anemia might account for their predisposition to bacterial invasion, especially by the salmonella organisms as mentioned above[715d]

A few isolated case reports have also indicated the increased susceptibility of patients with *splenic agenesis* to various recurrent infections including repeated bouts of the Waterhouse-Friderichsen syndrome[523] Splenic agenesis may be suspected by the finding of many Howell Jolly and Heinz bodies in the circulating erythrocytes along with target cells decreased osmotic fragility siderocytosis and leukocytosis in a patient with congenital heart disease (pp 189 and 426)[6, 4]

GROUP V

Infections—Specific

moniliasis, pyoderma gangrenosum, purulent conjunctivitis, and even exfoliative dermatitis[5,7]

An interesting feature of the congenital form of this disease, first noted by Janeway and his colleagues, is that approximately one half of these patients develop a unique type of arthritis after a number of years. The process is primarily one of a proliferative nature, with little destruction, pain, limitation of motion, or systemic features. It is regarded as a toxic synovitis resulting from the numerous recurring infections. Others have been intrigued by the very high incidence of what they consider to be true collagen disorders associated with this condition. These include rheumatoid arthritis, scleroderma, dermatomyositis, and generalized lupus erythematosus. This observation tends to refute the belief that gamma globulin antibodies are a significant factor in their pathogenesis.

Hypogammaglobulinemia has also been described in adults with various diseases affecting the reticuloendothelial or lymphatic systems, such as sarcoidosis, chronic lymphatic leukemia, and the lymphomas.[5,8,8,94] The profound urinary loss of these vital globulins in the nephrotic syndrome and its probable role in the predisposition to intercurrent infection was previously cited (p. 142)

the pure viruses in the near future as a result of their successful cultivation in tissue cultures uncontaminated by animal protein This technical achievement will facilitate the performance of many serologic and immunologic studies so that the diagnosis of viral infections will no longer have to be made either by exclusion or in retrospect weeks after specimens were submitted as has been the case in the past Clinicians must be wary about attributing too much significance to the level of the peripheral white blood cell count or the sedimentation rate as being indicative of either a bacterial or a viral infection

In general the manifestations of these diseases which have confused misled or surprised my colleagues, other authors, and myself will be specifically emphasized Certain infectious illnesses that characteristically involve multiple systems including tularemia streptococcosis, infectious hepatitis, and infectious mononucleosis are discussed elsewhere particularly under Groups III, IV, and XVII Others such as anthrax yellow fever bartonellosis and plague are omitted either because they are relatively easy to diagnose or because they are infrequently encountered clinically in this country Section VI of Part II, however contains a relatively complete listing of the useful and available studies in the bacteriologic and immunologic diagnosis of infectious disease, in which those infections not discussed in this chapter are included Aside from the fluid grouping of certain diseases under the general headings of the gram-negative bacilli, the systemic mycoses and the parasitic diseases, no rigid classification has been attempted in this chapter

TUBERCULOSIS

Hematogenous tuberculosis still remains the chronic infection to be considered above all in any unexplained chronic febrile disease [531] This is particularly important when the physical examination is repeatedly unrevealing and when one is dealing with either a racial group or patients with other chronic illnesses (especially diabetes mellitus malnutrition and certain forms of congenital heart disease) who are known to have less resistance to the tubercle bacillus The reactivation of tuberculosis during the course of prolonged steroid therapy was emphasized previously (p 142) In hospitals or clinics with a large percentage of Chinese, Negro or Indian patients all physicians soon become empirically sensitized to this diagnosis Clinicians must be ever cognizant of the current evolution of a predominantly tuberculin negative population in the United States which has concomitantly produced the problem of a population with no acquired resistance to this disease

In the postpartum patient who becomes febrile and extremely ill from unexplained cause the possibility of hematogenous dissemination must be entertained [53] Unfortunately sarcoidosis can also exhibit relapses after delivery In these patients however, the pregnancy has usually exerted a definite ameliorating effect on the associated multiple manifestations in contrast to the aggravating effect of gestation on tuberculosis [53 b]

One should *not* expect to see the so-called miliary lesions of the lungs early in the disease since the x ray cannot delineate lesions less than

Torulosis
Blastomycosis
Actinomycosis
Mucormycosis
Nocardiosis
Toxoplasmosis
Sporotrichosis

THE PARASITIC DISEASES
Amebiasis
Malaria

THE HELMINTHIC DISEASES
Trichinosis
Ascariasis
Hookworm Infestation
Visceral Larva Migrans
Schistosomiasis
Echinococcosis
Cysticercosis Cerebri

LEPROSY

RAT BITE FEVER
Spirillum minus *Streptobacillus moniliformis*

RELAPSING FEVER

CAT SCRATCH DISEASE

THE SPECIFIC infections listed in this section can all produce widely diversified patterns of disease that may defy accurate diagnosis for long periods of time Fever may be either low grade or absent particularly in the aged and when rectal temperatures are not taken As was indicated under the general discussion of pneumonia in the previous chapter, the consultant clinician in this antibiotic era is frequently forced to consider a number of nonbacterial infectious diseases which would have merited but little attention only a decade ago Furthermore many disorders of undetermined origin will undoubtedly prove to be due to or triggered by viruses and other infectious agents including a number of malignancies and the reticuloendothelioses

On the other hand a number of important infectious diseases are now encountered only very infrequently in most cities of the United States (viz diphtheria smallpox typhoid fever typhus fever) either because of active immunization or public health measures By the same token, such progress has resulted in a situation wherein an increasingly large proportion of physicians harbor no first hand experience in their detection Because of this diagnostic mistakes will be made that would not have been tolerated two decades ago

There is little doubt about the increasing availability of quantities of

ence of extrapulmonary caseonecrotic foci which may subsequently be responsible for hematogenous dissemination In this regard, attention must be specifically directed to the possibility of involvement within the genitourinary tracts (ovary tubes, kidneys, seminal vesicles, endometrial scrapings) followed by the surgical removal of any focus that is so discovered

Chest physicians have become aware of the significant incidence with which active pulmonary tuberculosis and primary bronchogenic carcinoma or Hodgkin s disease may coexist [535] In this situation, one might suspect the complicating lesion when the following are encountered the appearance of blood or other changes in the sputum, a persistent dull boring pain in the chest (especially after coughing) dyspnea out of proportion to the radiographic findings, progressive atypical pulmonary and hilar lesions in the absence of a positive sputum and clinical and radiologic deterioration while the patient is receiving chemotherapy Evidences of involvement of the phrenic nerve and the onset of a hypertrophic osteoarthropathy (p 325) can also indicate such a complication In view of the potential for surgical cure the clinician whose suspicion of complicating malignancy is aroused should promptly pursue his hunch with cytologic studies of the sputum, bronchoscopic examination, and even biopsy

Occasionally *the same tuberculous patient may concomitantly have an other bacterial or fungus disease* Even the same lymph node has been observed to be simultaneously involved in this manner [537] The high susceptibility of patients with Hodgkin s disease to tuberculosis will be discussed in a later chapter (p 182)

Phthisiologists also continue to remind us of the importance of regarding every patient with an unexplained *primary serofibrinous pleural effusion* as a potential case of pulmonary or hematogenous tuberculosis The institution of standard tuberculosis therapy is mandatory in young adults so affected, since it is repeatedly shown that up to 91 per cent will relapse or develop parenchymal disease if allowed normal activity (usually within a three year period) [538] Successful attempts have been made to achieve an early definitive diagnosis in these cases by means of pleural biopsy, either surgically or by employing the Vim Silverman needle (See p 797 in Section XI of Part II)

Clinicians should appreciate the fact that calcified and apparently dormant *tuberculous lymph nodes* in the hilus the mediastinum, and the abdomen may be of more than passing pathologic and roentgenologic interest In addition to harboring viable tubercle bacilli and serving as a potential source for both parenchymal and hematogenous dissemination, a variety of complications of varying clinical frequency are encountered These include the following the middle lobe syndrome, broncholithiasis, infection superimposed upon the bronchial stenosis compression of or rupture into the esophagus, pericardium, pleura lung stomach, or bowel, erosion of blood vessels with hemorrhage paralysis of various nerve structures (recurrent laryngeal, vagus phrenic sympathetic trunk), occlusion of the cisterna chyli and obstructive jaundice [539, 54]

The value of the anteroposterior lordotic radiographic position in the diagnosis of an atelectasis of the right middle lobe—as originally set forth by Fleischner—has been repeatedly affirmed [539c] It is pointed out that some

3 to 5 mm in diameter. Involvement of the liver, the spleen, and the bone marrow is usually far more extensive than that of the lungs. The spectrum of manifestations I have personally seen in this disease has included generalized lymphadenopathy, hepatomegaly with and without jaundice, divers blood pictures (leukopenia with a relative neutrophilia, leukemoid responses, hypersplenism), renal tract infection, abdominal pain due to the tuberculous mesenteric adenitis, meningitis, and pleural, pericardial, and peritoneal effusions. A disseminated, punctiform, papular, or vesicular eruption which may become hemorrhagic has been noted (p. 548). Competent hematologists and pathologists have made the diagnosis of a subacute myelogenous leukemia in patients actually suffering from hematogenous tuberculosis—a consideration that is well to bear in mind in patients who present themselves with atypical acute or subacute leukemic pictures.[533b] • Furthermore it is recalled that there were many reports in the older literature of terminal miliary tuberculosis in patients with true leukemic states.

An illustration of lupus miliaris disseminatus faciei appears in Figure 75 (Atlas page 47).

The author has been greatly impressed with the hematogenous spread of this disease, as evidenced by the large number (80 per cent or more) of positive bone marrow cultures he encountered in these patients at a large municipal hospital. This is also the experience of the others who have studied this subject.[533a] (It is of added pathogenetic interest that such cultures are often positive in patients with recent minimal pulmonary tuberculosis.) It should be realized that the tubercles encountered in the bone marrow of patients with hematogenous tuberculosis are usually not well differentiated.[533b] • Even in suspected instances of this form of the disease, tuberculin testing and culture of the gastric washings should not be neglected. While such cases have been reported, the rarity with which a true tubercle bacillus endocarditis is encountered stands in contrast to the frequency of the hematogenous dissemination of this organism.[533d]

The liver biopsy has consistently proved to be less time-consuming and equally diagnostic when the earliest institution of specific therapy is an imperative consideration.[534] More recently there has evolved the clinical concept of *'primary' miliary tuberculosis of the liver*, in which the tuberculous process appears to be confined to this organ for varying periods of time, apart from involvement of the lymph nodes or other organs.[535] • Should antituberculous therapy be instituted before a liver biopsy has been done, it can still be performed several weeks later, since recognizable tubercles often will persist at that time. This diagnosis merits considerable attention in the patient with unexplained pyrexia and a positive tuberculin test who also demonstrates hepatomegaly, splenomegaly, ascites or a "full" abdomen (contrasting with the wasting elsewhere) and unexplained anemia, leukopenia, elevated alkaline phosphatase (p. 87), and abnormal flocculation tests.

In the patient who has previously recovered from one episode of miliary tuberculosis as a result of therapy and subsequently exhibits a febrile course, one must consider the possibility of a *recurrent bout of miliary tuberculosis* (in contradistinction to a relapse of the disease).[536] • Reports of such instances make it incumbent upon the clinician to seek out the pres

used antituberculous drug, is the hyperuricemia and acute arthritis that may be induced in up to one fourth of the patients receiving it [545d]

INFECTIONS DUE TO THE "SAPROPHYTIC" ACID-FAST BACILLI

Before leaving the subject of tuberculosis, with the serious economic and prognostic stigmata immediately attached to this diagnosis the reader is reminded of the fact that the so-called "saprophytic" acid fast bacilli are on occasion isolated from chronic caseous granulomas in the skin, lungs bones and cervical nodes These lesions can closely resemble tuberculosis clinically histopathologically, and even roentgenographically The acid-fast organisms recovered, however are avirulent for guinea pigs and exhibit cultural characteristics quite different from the *Mycobacterium tuberculosis* (p 740) More specifically—and in contrast to the tubercle bacilli—these saprophytic acid fast bacilli grow more rapidly produce smooth and moist colonies easily emulsify in broth or saline solution, develop a pigment which is some shade of yellow, orange, or red, are more resistant or entirely resistant to PAS INH and streptomycin and may easily be re-isolated from the spleen by culture It is pointed out that even though these organisms are avirulent in guinea pigs, they can still sensitize these animals to tuberculin

In a well documented presentation of 19 such patients with cervical adenitis, recurring migratory chronic osteomyelitis and pulmonary infiltrations, Weed and his colleagues stressed the necessity of employing every means available to isolate these organisms and to distinguish them from tubercle bacilli in this clinicobacteriologic diagnostic dilemma [547] Florence has also made a comprehensive study of a number of cases in which chromogenic acid fast bacilli were found in the sputum and surgical specimens [548] The tendency for the pathologic processes produced by these atypical Mycobacteria to be localized and to spread primarily to contiguous tissues rather than to distant structures was noted

Although there are marked differences in the response of the "yellow acid fast bacillus to the antimicrobial agents when compared with the tubercle bacillus, clinicians must not be too hasty in separating this species and the diseases it produces from tuberculosis at the present stage of our knowledge

The nontuberculous causes for pulmonary cavitation were considered at length in the previous chapter (p 131)

STAPHYLOCOCCAL INFECTIONS

All clinicians should harbor considerable respect for culture reports returned with the finding of *Micrococcus pyogenes* var *aureus* This is particularly important when dealing with infection in such vulnerable metastatic sites as the bones, kidneys endocardium lungs meninges brain skin, liver and spleen [491, 549] It has been aptly observed that the staphylococcus is replacing the pneumococcus as the notorious invader in terminal illness Staphylococci are particularly prone to invade such areas as the sites of needle punctures bedsores and inlying cannulas A culture report

difficulty might arise in distinguishing this entity from the less frequently encountered mediastinointerlobar pleurisy with effusion in which this same area is involved

In the presence of an aneurysm of the aorta of obscure origin, with or without demonstrable calcification in the mesenteric nodes, the possibility of a mycotic aneurysm resulting from either a tuberculous para aortic lymphadenitis or a tuberculous aortitis might well be entertained[543] At least one instance of a dissecting aneurysm of the aorta secondary to a tuberculous aortitis is on record[543c]

Several of the problems related to the evolution of *antibiotic resistant organisms* in tuberculosis are taken up under Group XV (p 452) It will suffice for the present to point out that while in certain instances some difference of opinion as to the pathogenicity of drug resistant tubercle bacilli exists, it appears likely that the number of resistant strains will increase as a greater percentage of patients are being treated at home, and as more drugs are introduced in the treatment of tuberculosis

The magnitude of this particular problem is shown by the finding of tubercle bacilli that were resistant to one or more antituberculous agents in 11 7 per cent of patients (among those found to have positive sputa) who were recently admitted to four tuberculosis hospitals *for the first time*[545a] It would not appear at present that isoniazid resistant tubercle bacilli pose as serious a problem as streptomycin resistant organisms Nevertheless note must be taken of the fact that many tuberculosis centers are now encountering an incidence approaching 10 per cent of newly admitted patients who had never received such therapy yet whose initially cultured organisms prove to be resistant to 5 mcg per cc of INH[545b]

With the increasing emphasis upon the outpatient treatment of pulmonary tuberculosis physicians caring for patients under these circumstances must be constantly alerted to the numerous diverse *hypersensitivity reactions and other side effects from the antituberculous drugs employed*—most notably para aminosalicylic acid (PAS, aminosalicylic acid) and isonicotinic acid hydrazide (INH isoniazid) Otherwise, they might well be regarded as evidences of tuberculous complications For example fever, eruptions, lymphadenopathy hepatosplenomegaly the Loffler syndrome, and toxic hepatitis have been observed with PAS[4 544]

A fatal methemoglobinemia and acute hemolytic anemia has resulted from the administration of stock solutions of PAS which had decomposed in the course of prolonged standing[544c]

Similarly INH has caused fever dermatitis, arthralgia purpura, central nervous system symptoms and peripheral neuritis (in large measure due to the induced pyridoxine deficiency)[137 380 545] The evidences of the nervous system involvement in instances of isoniazid toxicity have included diplopia vertigo paresthesias, headaches, hyperreflexia mood disturbances and optic neuritis and atrophy[545a] They may be obviated to a large degree by the concomitant administration of pyridoxine, especially in chronic alcoholics, other malnourished individuals and those patients with pre-existing cerebral damage—these being factors which appear to predispose to the neurotoxic effects of this drug

One of the interesting side reactions of *pyrazinamide*, a less commonly

at this stage Unusual fever or transient alarming systemic features occurring shortly after the institution of penicillin therapy (in a patient who turns out to have a positive serology) might be explained by the Herxheimer reaction An obscure remittent or intermittent fever in the presence of a positive serology, or an unexplained tumor found under similar circumstances may be due to tertiary syphilis A course of penicillin therapy serves as a good therapeutic test in such cases (p 814)[553]

The old dictum stating that ulcers or lesions of the skin which present the triad of induration chronicity, and a satellite adenopathy—even when they appear in the extragenital areas—should be regarded as luetic until proven otherwise is always valid There is considerable evidence supporting the close relationship between tertiary syphilis and cancer of the tongue[553c] It is never superfluous to stress that the diagnosis of latent syphilis presupposes the existence of a negative spinal fluid examination

An illustration of secondary syphilis appears in Figure 78 (Atlas page 49) The cutaneous manifestations of late syphilis are depicted in Figures 22 and 33 (Atlas pages 13 and 21)

The *Treponema pallidum* immobilization test and its simpler modifications (most notably the *Treponema pallidum* immune adherence test) have proved valuable in separating patients with latent syphilis from those whose *biologic false positive reactions* may represent an even more serious systemic disease, particularly disseminated lupus erythematosus[554] Systemic disease was pre ent in 21 6 per cent of 555 patients with biologic false-positive reactions studied by Miller Brodey and Hill Among this group systemic lupus erythematosus diseases of the liver rheumatoid arthritis rheumatic heart disea e, and diabetes mellitus were the ones most commonly encountered[555d]

When such a false-positive reaction is suspected, certain simple tests that may be influenced by abnormal globulins are in order—most notably the sedimentation rate the cephalin flocculation and thymol turbidity tests, and protein partition studies In this regard, however it would be wise to heed Miller s caution of accepting with great reluctance the statement that sarcoidosis frequently causes a false-positive serology[555a] These studies are also of great potential value in diagnosing syphilis under the following two situations (1) when confronted with negative blood and spinal fluid serologies in patients with clinical evidence of this disease, most notably in late syphilis and (2) in mothers with negative serologies whose children develop the stigmata of congenital syphilis[555b]

LYMPHOGRANULOMA VENEREUM

Another venereal disease that may evoke serious extragenital and systemic responses is lymphogranuloma venereum Its sequelae of rectal strictures and genital elephantiasis following the stellate abscesses are not infrequently seen in Negro clinics, particularly in the southeastern sections of the United States This infection can produce a lymphocytic meningitis keratitis conjunctivitis generalized skin eruptions erythema nodosum ulcerative colitis,[172] polyarthritis pericarditis and splenomegaly—in addition to the inguinal or femoral buboes and obscure fever[556 558] In fact the

of *Staphylococcus albus* does not usually carry these serious pathogenetic implications The coagulase and hemolysin characteristics are much more important than the pigment properties, however

The diagnostic and therapeutic problems of staphylococcal superinfection (p 139), spinal epidural abscess (p 134), and pulmonary, renal and cerebral abscesses (pp 121, 109, and 133) due to the staphylococcus are discussed elsewhere, as indicated The many clinical variants and therapeutic considerations in staphylococcus septicemia and endocarditis have been ably reviewed by Rogers and by Wilson and Hamburger[549]

There is an undeniable increase in the incidence of hospital personnel (and patients with noninfectious conditions) who are becoming carriers of *pathogenic antibiotic resistant staphylococci*[550, 551] This is at least partly responsible for the occurrence of serious infection with these organisms in the postoperative, postpartum and neonatal periods One method suggested for controlling this phenomenon is the limitation of the use of certain antibiotics (such as erythromycin and chloramphenicol) in hospitals in order to preserve their full effectiveness against such resistant staphylococcic infections The discrepancy between the great sensitivity of these organisms to the bactericidal antibiotics *in vitro* and the clinical resistance (or even death) encountered in patients so invaded who receive these drugs should cause the clinician to prognosticate with much caution Perhaps this paradox is explained by the "sanctuary" that pathogenic staphylococci appear to obtain temporarily within the phagocytosing leukocytes or monocytes[550b] At the present time the combination of chloramphenicol and erythromycin appears to have the most deterrent effect upon the *in vivo growth of penicillin resistant staphylococci*

In the absence of an endocarditis, a micrococcal bacteremia is most frequently noted following a transurethral resection[40 b] The importance of this distinction and the seriousness of staphylococcal endocarditis are underscored by the continuing mortality rate of over 50 per cent notwithstanding the intensive and skillful use of all the antibacterial agents currently available[549c]

SYPHILIS

Syphilis must be cited to remind clinicians that the original "great mimic" is still not obsolete and that there is a reservoir in *every* community that cannot be completely eradicated In this age of penicillin and "enlightenment," it is paradoxic that public health officials continue to be alarmed at the apparent rising incidence of syphilis with its long term sequelae, and the occurrence of epidemics even in previous low prevalence areas[55 c] They attribute this phenomenon in large measure to the following combined factors (1) a lessened index of suspicion (2) inadequate therapy and (3) the laxity in carefully following individual patients As an example of the de-emphasis on control programs the Joint Committee on Accreditation of Hospitals in January 1956 dropped the requirement that all patients on admission should have a serologic test for syphilis[552]

The constitutional symptoms and dermadromes of secondary syphilis are too numerous and variant to set forth here (See p 549) It is indeed fortunate diagnostically that the blood serology is almost always positive

Only agglutinin titers which are greater than 1:160 and which increase under observation are generally considered significant (p. 741). While such a brucella agglutinin titer is desirable in the suspected case of chronic brucellosis in whom blood cultures are sterile, low titers may be encountered which are the result of "blocking" antibodies. Where this phenomenon is suspected, centrifugation of the tubes at the conclusion of the test might result in the finding of a significant titer (p. 741).[560]

It has been emphasized that all undiagnosed granulomatous material removed at the time of surgery should be kept sterile and cultured for the brucellae.[564a] This is particularly important when dealing with lymph nodes and nodules from the spleen, liver, or lung with or without areas of calcification.[561] Whereas suppurative complications are infrequently encountered in brucellosis due to *B. abortus* (actually the least invasive of the three species of the brucellae), the occurrence of chronic suppuration, caseation, and calcification in this disease is highly suggestive of infection caused by *B. suis*.[561c] It is very probable that the successful treatment of this infection accelerates the calcification of the brucellar lesions in the liver.

LEPTOSPIROSIS

The appreciation of leptospirosis as a significant entity in the diagnosis of subacute infectious illness has come a long way since the classic teachings concerning Weil's disease only a decade ago.[565] With the more recent availability of specific diagnostic sera, the several strains of this spirochete have been unexpectedly found as frequent causes for "benign aseptic meningitis," even without any evidence of involvement of the liver or kidneys.[473]

Other neurologic complications of the leptospiroses include subarachnoid hemorrhage, paralysis of the various cranial nerves, brachial and sciatic neuritis, transverse myelitis and bulbar paralysis. In the absence of a concomitant intense and prolonged icterus, the finding of xanthochromia and pleocytosis in the spinal fluid is more characteristic of this disease than infectious hepatitis or the other causes of jaundice.

Hepatosplenomegaly and jaundice are actually relatively uncommon in areas where the incidence of the *Leptospira icterohaemorrhagiae* strain is infrequent. (*Lept. australis A* and *Lept. bataviae* are also likely to cause severe hemorrhagic disease.) Even so, the presence of conjunctivitis, lymphadenopathy and a normal white blood cell count with a neutrophilia have proved valuable in differentiating leptospirosis from other acute illnesses, especially dengue fever.

The various modes of transmission of these infections are indicated by such descriptive designations as swineherd's disease (*Lept. pomona*), canicola fever (*Lept. canicola*) and water or mud fever (*Lept. grippotyphosa*). It is accordingly wise to bear these entities in mind when obscure illness affects sewer workers, abattoir workers, poultrymen, swimmers, fish cutters, veterinarians and farmers. Furthermore, leptospirosis is widespread in a number of states throughout the country, particularly in North Carolina.

other symptoms may be so severe that slight lymphadenitis could be completely overlooked or disregarded The hypergammaglobulinemia, the Frei test (p 748) and the complement fixation titer (p 744) are all helpful in establishing this diagnosis [555, 559] A contaminated enema tip has been reported as an unusual source of this infection

BRUCELLOSIS

The diagnosis of brucellosis is always debated when a case of prolonged unexplained fever occurs in one of the several large areas of the country where this disease is not commonly seen It is not surprising that the most frequent erroneous diagnosis is influenza when one considers that the symptoms of weakness sweats, anorexia generalized aches headache, nervousness and mental depression are so outstanding Aside from anorexia there are usually few gastrointestinal symptoms in brucellosis The fever in brucellosis frequently exhibits a nonspecific spiking character being maximal late in the afternoon and evening and then decreasing in the early morning hours

Occasionally such complications as arthritis spondylitis endocarditis meningoencephalitis orchitis prostatitis, splenomegaly (with or without calcification thrombocytopenia or a hemolytic anemia) and hepatitis can produce striking localized manifestations [560, 561] The widespread unawareness of acute and chronic pulmonary brucellosis was recently pointed out by Greer in a review of 41 cases with this feature [435a] The chest films in these disorders commonly reveal pneumonitis bronchopneumonia localized granulomas bronchial obstruction, pleural thickening and marked perihilar thickening with peribronchial infiltrations The caseous granuloma in the lung resulting from chronic localized infection due to *Brucella suis* may be indistinguishable from that caused by the tubercle bacillus both histologically and by x ray [435b]

It would be well to remember this disease in illness affecting veterinarians farmers meat packers and butchers who come in contact with cattle, since the low virulence living strain of *Brucella abortus* (strain 19) that is being used country-wide to immunize cattle is probably pathogenic for man [560d] Brucellosis has even been transmitted by blood transfusions [562]

In view of the importance of obtaining unequivocally positive bacteriologic confirmation—if at all possible—before making this diagnosis, cultures of clotted blood and of bone marrow aspirations might prove to be most helpful In one experience with 228 patients having active brucellosis an average of seven blood cultures per patient were needed to ensure at least one positive culture in the pretreatment observation period [560c] The brucella organisms grow better in liver infusion broth and under decreased oxygen tension See Part II (p 736) Although the granulomas in the marrow are not characteristic histologically the incidence of positive cultures has been considerable, in contrast to the results obtained from cultures of the peripheral blood [560, 563] Even where there is no evidence of liver involvement in the suspected case of brucellosis, it is possible to isolate and culture the *B abortus* organism by percutaneous needle biopsy of the liver [564b] The histologic changes of such liver specimens may be of added value

chemotherapy and antibiotics (to which the organism is fortunately quite sensitive) and the difficulty in culturing the organism unless the proper media and anaerobic techniques are employed

In addition to the fever and headache, a true arthritis, severe pains in the muscles and feet and splenomegaly are typically present Crops of skin eruptions commonly occur and may consist of macules, papules, nodules, vesicles, and purpuric lesions The characteristic petechial hemorrhages of meningococcemia can be found not only in the skin over the extremities and the mucous membranes of the mouth and eyes, but also on the palms and the soles (The latter distribution might facilitate the diagnosis in Negroes since the skin is usually less pigmented there) Occasionally, the course is further complicated by pneumonia, endocarditis, ophthalmitis conjunctivitis progressive nephritis, gastrointestinal hemorrhage, eye muscle or facial paralysis, and hearing loss [572]

The *Waterhouse Friderichsen syndrome* (dyspnea, cyanosis, cutaneous eruption, and fulminant peripheral circulatory collapse from acute adrenal failure) is *not* specific to meningococcemia [573] Furthermore, it is quite probable that the shock in these infections is related more commonly to the toxic, hypovolemic, and hypotensive sequelae of both the bacteremia and the associated endotoxin production than to actual adrenal insufficiency [574, 575] With reference to the latter, it is of interest that chronic adrenal insufficiency is not encountered in patients with acute meningococcic septicemia and peripheral vascular collapse who survive because of modern therapy [573]

The cutaneous manifestations of meningococcemia are depicted in Figure 79 (Atlas page 50)

CHRONIC GONOCOCCAL SEPSIS

Chronic gonococcal sepsis was recognized more often before the antibiotic era as a cause of obscure prolonged fever The characteristic temperature curve described consists of a double spike on each of several consecutive days [576] Even in the absence of reinfection, gonococcal infection may remain dormant for many years

The manifestations of this disorder include an endocarditis extensive skin eruptions (keratosis blennorrhagica hemorrhagic, vesiculopustular and bullous lesions), polyarthritis, tenosynovitis, perihepatitis conjunctivitis, and meningitis [577] The endocarditis exhibits most of the cardiac embolic nephritic, and arthritic features characteristic of streptococcal endocarditis [408, 409] Recovery of the gonococcus from the blood may be very difficult, however even when special media are employed and when the cultures are incubated under increased carbon dioxide tension

An illustration of keratosis blennorrhagica appears in Figure 80 (Atlas page 50)

Although gonorrheal arthritis is usually monoarticular and roentgenographically similar to the other types of infectious arthritis, there are several findings on x ray that might alert one to this entity These include the following (1) localized destruction of the cartilage on the under surface of the patella, with subsequent hypertrophic changes both on its margin and

MUMPS

Much the same recent appreciation of its incidence and variform clinical manifestations holds true in the case of mumps as in leptospirosis, particularly as it relates to the frequent misdiagnosis of "nonparalytic poliomyelitis"[568c] After having seen such complications of this disease as severe chronic labyrinthitis, persistent Bell's palsy, permanent deafness, and the more common orchitis and pancreatitis—even in the absence of a significant parotitis—the author has developed considerable diagnostic respect for this "childhood" disease

Arthritis, mastitis, epididymitis, purpura, pericarditis, myocarditis, hepatitis, thyroiditis, and serositis also are documented as manifestations of mumps[566-569] A nontender presternal swelling is occasionally associated with severe submaxillary gland swelling which interferes with the lymphatic drainage of the upper sternal area[570] (This phenomenon may also be observed in malignant lymphoma when the subcutaneous lymph drainage of the anterior chest wall to the deeper subpleural and intermuscular vessels is impeded by sternal and retrosternal involvement)[570b]

Considerable progress is being made in improving laboratory means of detecting and confirming the diagnosis of mumps In this regard, specific reference is made to the distinctive cytopathogenic effect of the mumps virus in tissue cultures of monkey kidney cells[568b]

To one who is not familiar with the entity of bilateral hypertrophy of the masseter muscles, considerable confusion in the diagnosis of "chronic mumps" could be encountered[571] While *benign masseteric hypertrophy* may be of the congenital or familial type (producing the "chipmunk look" when it occurs on a thin or bony face), by far the majority of these cases are of the acquired type[571] In the latter instance it is caused by the habitual clenching or grinding of the teeth in tensed patients—a habit that often persists during their sleep The occasional instance of unilateral hypertrophy that results from chewing on only one side or from the habit of "cradling" the jaw in the hand may give more difficulty when the question of mumps is raised The other misdiagnoses of this not infrequent benign disorder include mixed tumors of the parotid gland, lipoma, rhabdomyoma, and external otitis

Similarly "iodide mumps" resulting from intravenous urography should be borne in mind in unusual cases of parotitis[1184] In an earlier chapter, reference was made to the occurrence of a chronic, asymptomatic and noninflammatory enlargement of the parotid gland that is commonly observed in alcoholic patients with cirrhosis of the liver and in other instances of malnutrition (p 85)[320b] * The periodic swelling of the parotid glands in the Sjogren-Mikulicz disease should not be diagnosed as "recurrent mumps" (p 414)

MENINGOCOCCEMIA

Chronic meningococcemia without meningitis is mentioned to remind the reader that this entity is still with us even though it is hardly ever recognized This circumstance is due in large measure to the widespread use of

toid, impetiginous vesicular, pustular, bullous, ulcerative, and gangrenous—has been encountered and is frequently followed by paralysis (p 550) The diagnosis of diphtheria must not be overlooked in unexplained cases of myocarditis heart failure, nephritis, and polyneuritis [582] Unfortunately, the author has recently shown that once the exotoxin has become fixed to the tissues and paralysis has occurred, a beneficial response to corticotropin or steroids similar to that obtained in the Guillain Barré syndrome cannot be expected [583] Several observers have noted that there appears to be a greater incidence of diphtheria in the histories of patients with heart block and other conduction defects than might otherwise be expected [584]

The cutaneous manifestations of diphtheria are depicted in Figure 88 (Atlas page 57)

ERYTHEMA MULTIFORME EXUDATIVUM

The entity of erythema multiforme exudativum, resulting in "the mucocutaneous-ocular syndromes' with their numerous eponymic variants (Stevens Johnson Behçet, Reiter von Hebra Klauder)—so-named as the skin, eyes oral cavity and genitals are variously affected—has served amply to compound the clinician's confusion on many occasions [585, 586] The list of those diseases it frequently mimics includes rheumatic fever (especially erythema marginatum), erythema nodosum lupus erythematosus pemphigus erythema multiforme (no cropping usually occurs here) drug eruptions and the other exanthematous diseases (particularly "chickenpox that lasts too long) The pulmonary complications of erythema exudativum multiforme were considered in the previous chapter (p 126) [586c]

Reiter s Syndrome

In view of these manifold variations and symptom complexes the patient is often first seen by a specialist in one of many fields In the so-called Reiter's syndrome, for example one usually encounters a benign and self limited disorder characterized by a urethritis and prostatitis (but no epididymitis), an explosive inflammatory polyarthritis (particularly of the ankles, knees and wrists) and a mucopurulent conjunctivitis A very similar clinical picture has been encountered in the case of the acute hemorrhagic cystitis urethritis, and prostatitis associated with pleuropneumonia like organisms (p 113) [401] The less common manifestations of Reiter s disease include keratodermia blennorrhagica balanitis circinata costovertebral angle tenderness and prolonged auriculoventricular conduction Correct diagnosis is most important in view of the beneficial effects of steroid therapy

An illustration of keratosis blennorrhagica appears in Figure 80 (Atlas page 50)

PSITTACOSIS AND ORNITHOSIS

Any discussion of the specific infectious diseases should include the increasing problem of psittacosis and ornithosis As indicated under Group

on the adjacent femur, (2) small localized areas of rarefaction in the bone at the junction of the articular surface and cortex, and (3) the deposition of new bone (spurs) along the tendinous attachments This specific arthropathy should be suspected when a migratory or localized arthritis follows trauma to the prostate, the urethra, or the pelvic organs Notwithstanding the emphasis placed on the gonococcal complement fixation test in some centers (p 712)[578] most authorities view the reliability of this procedure with much skepticism

HERPES SIMPLEX INFECTIONS

The subject of infection with the virus of herpes simplex connotes considerably more to students of infectious disease than the familiar recurrent lesions about the mouth acute herpetic gingivostomatitis genital herpes and primary keratoconjunctivitis[579] While the diagnostic cellular features seen in the cytologic study of the vesicular and bullous lesions are also found in herpes zoster and in varicella they do not occur in the other types of vesiculating eruptions The meningoencephalitis associated with the presence of a 'benign aseptic meningitis due to this "orphan" virus was previously cited (p 135) The viremia in newborn infants caused by herpes simplex is characterized by a vesicular eruption, jaundice, pneumonitis and profound toxemia

Esophageal herpes is observed in a surprisingly large number of patients with cancer of adjacent organs who had been subjected to trauma of the esophagus either by irradiation operation or prolonged tube feeding[580] Attention is also directed to the entity of eczema herpeticum or Kaposi s varicelliform eruption which may closely simulate severe smallpox eczema vaccinatum, and varicella It is caused by the virus of herpes simplex and occurs most frequently in patients with atopic dermatitis Here again, the finding of the characteristic multinucleated giant cells and inclusion bodies within each nucleus from biopsies of the skin serves to rule out variola

An illustration of Kaposi s varicelliform eruption appears in Figure 19 (Atlas page 12)

DIPHTHERIA

A number of diagnostic problems are continually posed by unrecognized diphtheria This is particularly true when the infection starts in the nose larynx or skin and where the membrane is not seen or initially recognized In many instances therapy with the antibiotics (but without the early administration of antitoxin) has served only to mask and possibly enhance the subsequent serious complications Even though the Klebs Loffler bacillus is sensitive to penicillin and the broad spectrum antibiotics, the exotoxin is not neutralized by these agents Notwithstanding the general impression to the contrary diphtheria is *not* a rare disease in fact, it has become more common in the older age groups because fewer people have been exposed in childhood[581]

Acute or chronic cutaneous diphtheria of many descriptions—eczema

the rickettsioses encountered in the United States appear to be susceptible to the broad spectrum antibiotics

INFECTIONS DUE TO THE GRAM NEGATIVE BACILLI

Typhoid Fever

It is indeed a gratifying commentary on the tremendous progress of preventive medicine during the past few decades that has resulted in the diagnostic problem which sporadic cases of typhoid fever now create In spite of the fine epidemiological control methods existing in our country, however, this disease still remains a constant threat One should not be misled by a well documented history of previous immunization Some vaccinated individuals can acquire the infection with or without symptoms or they may even become chronic carriers [590]

Fever, coryza, cough, 'rose spots, headache, diarrhea or constipation, slight splenomegaly and leukopenia constitute the classic description of this disease Various extraintestinal complications may occur, among which periostitis, arthritis, cholecystitis pneumonitis (p 123), thrombophlebitis, abortion, and chronic pyelonephritis merit particular attention [434 591]

The cutaneous manifestations of typhoid fever are depicted in Figure 76 (Atlas page 47)

In the absence of either the isolation of the organism by culture or the changes in the blood Widal test (p 747) such diagnoses as hematogenous tuberculosis typhus fever, psittacosis, infectious mononucleosis brucellosis, atypical pneumonia, salmonellosis, tularemia malaria infectious hepatitis, and lymphoma should merit consideration when a typhoidal picture presents itself Of the salmonellae, *Salmonella paratyphi A* and *B* and *S panama* are most likely to produce a typhoid like picture In contrast to the infection due to *S typhi*, however, there is usually a high pulse rate and an elevated white cell count with a shift to the left [59]

Salmonellosis

Another group of bacterial infections that has become increasingly appreciated for its elusiveness, frequency morbidity, and even mortality is that of salmonellosis Not only do the gastroenterocolitis and typhoid like syndromes occur but a bacteremia and septicemia may take place with or without localization in the meningeal, renal, pulmonary endocardial bone and joint gallbladder, peritoneal and pleural sites A salmonella bacteremia can also produce both miliary lung lesions and a spondylitis [596b] The invasiveness, the rarity of gastroenteritis, the high incidence of septicemia (with or without focal manifestations) and the occasional rose spots and splenomegaly in infections due to *S choleraesuis* and *S paratyphi C* cause them to resemble typhoid closely [59]

Saphra and Winter have reported 318 fatalities among 7779 human salmonella infections reported to the New York Salmonella Center [593] In several reports of other infectious diseases (viral hepatitis relapsing fever) a complicating or coexisting infection with salmonella or shigella organ-

IV, in the presence of a severe protracted febrile illness with an atypical pneumonia, splenomegaly, and thrombophlebitis, these conditions must be borne in mind (p 125)[587] The clinical and radiographic manifestations of psittacosis are extremely variable, as is the course of this disease A variety of infectious and noninfectious diseases may be simulated, including Q fever, influenza, bacterial pneumonia, infectious hepatitis, subacute bacterial endocarditis rheumatic fever, sarcoidosis, typhoid fever, and carcinoma of the lung[588]

The great popularity of parakeets and other psittacine pets, along with the laxity in enforcement of the laws relative to their importation and transport since 1951, have significantly contributed to the increased incidence of this disease Furthermore, there is a large reservoir of the infection among nontropical North American birds and domestic fowl The so-called 'New York dressed birds (i e, not eviscerated at the time of processing) are of particular hazard to the public in this regard Sick parakeets have been converted into apparently well carriers of psittacosis by the practice of adding one of the tetracycline antibiotics to their drinking water

THE RICKETTSIOSES

No detailed discussion of the rickettsioses will be entered into here, other than to make brief mention of the necessity for considering the diseases caused by these obligate, intracellular, pleomorphic organisms in obscure febrile illness with an associated exanthem Since rickettsiae may persist in apparently healthy individuals for years (in light of recent histologic studies on infected lymph nodes), it is possible that man actually can serve as an interepidemic reservoir for these diseases[589] In Rocky Mountain spotted fever, murine typhus epidemic typhus, and rickettsial pox the varying prodromal states (malaise, headache, anorexia) are followed by chills fever generalized aching cough, splenomegaly, meningismus, and the characteristic eruption Their courses may be further complicated by thrombosis of major blood vessels peripheral vascular collapse, renal failure, necrosis of the skin gangrene of the digits, pneumonitis hypochloremia, and various neurological changes

Rocky Mountain spotted fever has now been reported from practically all areas in the United States It is endemic not only in the Rocky Mountain states, but also in the South Atlantic states Discrete macules on the palms and soles can usually be found early in this disease, even in dark skinned individuals in whom the eruption might otherwise be difficult to detect

Both careful inquiry into and the search for contact with rats lice mites, and ticks is obviously of potential decisive value to the alerted physician The importance of considering Q fever in unusual cases of atypical pneumonia (p 125) and acute liver disease (p 92) was previously mentioned A detailed analysis of the diagnostic serologic procedures in this group of infections (the Weil Felix and the complement fixation reactions) is presented in Section VI of Part II (p 745) Fortunately all

the respiratory tract during penicillin therapy An *E coli* septicemia is not infrequently complicated by a meningitis, a suppurative arthritis, herpes labialis, and metastatic pyogenic infections involving the skin kidney, liver, spleen, or endocardium[598]

The *clinical significance of the bacterial population in the bowel* is clearly shown in several independent studies dealing both with the mechanism of shock and with the ammonia intoxication occurring in hepatic coma The profound and beneficial effect of oral neomycin therapy in a number of these cases highlights the importance of these observations (p 97)[353 574]

The endotoxins elaborated by many of the gram negative organisms have a great tendency to produce not only high fevers but also a severe type of shock (These bacterial toxins produce widespread vascular changes resulting in both an uncompensated expansion of the vascular capacity and a relative reduction in the effective blood volume, due in large measure to the pooling of large quantities of blood in the portal and splanchnic venous beds)[599] Only the awareness of this phenomenon and the importance of the associated hypotension can alert physicians to institute therapy early, since the usual evidences of vascular collapse may be either absent or obscured by the warm skin the bounding pulse and the fever[600] Notwithstanding the vigorous treatment of the underlying infection and attempts to maintain the blood pressure, a significant number of patients with this type of bacteremic shock will still develop renal ischemia and insufficiency which often proves to be fatal[575]

Other gram negative pathogens which are less commonly encountered—but still very significant clinically—include the proteus and bacteroides bacilli, *Alcaligenes faecalis* and *Pseudomonas aeruginosa* (or *Bacillus pyocyaneus*) In addition to the evidences of sepsis and circulatory collapse produced by this group of infections, pseudomonas bacteremia is occasionally characterized by several distinctive features A typical skin eruption (termed ' echthyma gangraenosum) may be noted commencing as macules or vesicles and then becoming pustular or even developing into necrotic ulcers The anogenital region and the axillae are likely to be the sites of such metastatic lesions[484] Thrombocytopenia and agranulocytosis have also been associated with *Ps aeroginosa* infections The serious meningeal complications of this opportunist organism particularly following spinal puncture or spinal anesthesia were discussed in the previous chapter (p 137)

Although this text does not emphasize therapeutics it is appropriate to stress the potentially misleading inferences of the antibiotic sensitivity studies in this particular group of gram negative bacteremias and to cite the necessity for much therapeutic judgment when confronted with the increasing incidence of *in vitro* resistance The combination of streptomycin and a tetracycline antibiotic has often proved curative in such a situation, notwithstanding laboratory reports of resistance to these agents

Bacteroides Infections

The gross neglect of the clinical significance of infection caused by certain anaerobic, nonsporing and pleomorphic gram negative bacilli classi

isms was found (p 177) A generalized or focal activation of salmonellosis in the form of abscesses, osteomyelitis, meningitis, and the like have followed trauma antibiotic therapy steroid therapy, or some unrelated pathologic process [59 a]

A few brief comments pertaining to the epidemiology of this disease are in order The excretion of salmonella organisms persists for weeks or even months in at least one fifth of these cases, even after the return of normal bowel function [59 a] Only the rigid supervision of the processing of egg poultry and meat products (similar to the insistence upon uncontaminated dairy products by public health officials) can eliminate them as frequent sources for the dissemination of salmonella organisms Another potential vehicle for the dissemination of salmonella organisms is perishable smoked fish (whitefish, lox) which some markets display outside of refrigerators The light smokes and salts employed do not preserve them [594b]

Nosocomial salmonella gastroenteritis has also resulted from the use of tube-feeding mixtures that were made with commercial yeast which had been contaminated with these organisms [594a] Another related problem in hospitals is the occurrence of a salmonella enteritis following gastric surgery the symptoms of which might readily be ascribed to the disturbed postoperative physiology This issue is particularly apt to arise after a vagotomy [595]

Bacteriologic diagnosis is often made difficult or even impossible by the premature institution of antimicrobial therapy, by the many varieties of salmonellae and by the paucity of commercial diagnostic preparations that can detect antibodies to the somatic antigens of Groups B, C, D, and E (which produce the majority of infections in this country) [596] The knowledge that almost one-half the cases of human salmonellosis in the United States are due to the C group should be of considerable interest to public health officials This is because the standard T A B vaccine induces an immunity only to Groups A (which is rather rare here), B and D—but *not* to Group C [59 a]

The results of observations in those laboratories in which typing of salmonellae is routinely done show the surprising frequency with which patients who are infected with these organisms are found to be harboring more than one type For example in one special study of 130 fecal specimens from 75 individuals who were known to be excreting salmonella organisms multiple types were found in 13 (17 3 per cent) [59 c]

Bacteremia Caused by the Other Gram Negative Bacilli

Bacteremia caused by the other gram negative bacilli is a most important complication of surgery or instrumentation particularly when dealing with the genitourinary tract (transurethral prostatic resection retrograde pyelography cystoscopy) Cirrhosis of the liver and diabetes mellitus appear to increase susceptibility to this type of bacteremia In a series of 137 such cases (exclusive of typhoid fever brucellosis and endocarditis), *Escherichia coli* and *Aerobacter aerogenes* were the responsible organisms in 100 patients [501 597] Even in the absence of aspiration *E coli* may invade

Histoplasmosis may likewise exhibit a disseminated fatal course, particularly in the very young and old This complication is characterized by fever anemia, marked weakness, pneumonitis (p 124), hepatosplenomegaly, and an ulcerative enteritis with enlarged mesenteric lymph nodes [605] Here again, the organism can frequently be conveniently and successfully obtained from the bone marrow Localized ulcers in the mucous membranes of the upper alimentary or respiratory tracts also occur The adrenal glands may be destroyed by this disease, giving rise to adrenal insufficiency [605] The association of histoplasmosis and lymphoma has been documented in 25 cases [607] Dissemination can also be initiated by cortisone therapy [21b]

The cutaneous manifestations of histoplasmosis are depicted in Figure 86 (Atlas page 56)

Even in areas considerably removed from the recognized endemic regions in the central states, histoplasmosis has followed exposure to dust contaminated by the excreta of chickens pigeons, and bats in such places as chicken houses abandoned buildings, silos, and church belfries The resulting atypical pneumonia can be conclusively shown to be due to this disease by the development of a positive reaction to the histoplasmin antigen and thereafter of disseminated pulmonary calcifications [435 606]

Torulosis

At this point attention is directed to the problem of torulosis (cryptococcosis) This disease may not only involve the lungs, the skin and the subcutaneous tissues but also the central nervous system in the form of a chronic lymphocytic meningitis which closely resembles that caused by tuberculosis (p 136) [608] The osseous involvement is often widely disseminated with a tendency to involve bony prominences The latter lesions are generally osteolytic and incite very little bone reaction [610a] The cutaneous pustules due to torulosis may resemble myxomatosis tumors

The presence of this fungal disease—especially when widespread—should make one diligently search for an underlying or associated lymphoma most notably Hodgkin's disease and reticulum cell sarcoma [609] This sequence has already proved to be the case several times in the author s own experience Cryptococcosis has also been associated with granulocytic leukemia lymphocytic leukemia monocytic leukemia, congenital hemolytic anemia and multiple myeloma [611]

Blastomycosis

The subject of North American blastomycosis was recently reviewed by Kunkel and Sutliff who have reported on 91 and 25 cases of this disease respectively [61] The chronic involvement of the lungs, skin bones and genitourinary systems has been stressed in these papers Pulmonary blastomycosis tends to disseminate postoperatively, especially if no previous hydroxystilbamidine was given to the patient The organism could also be repeatedly obtained from the sputum of a patient presenting himself to the author for a chronic ulcer and osteomyelitis on the dorsum of the foot

fied under the genus *Bacteroides* has been impressively shown in recent reports of 47, 35, and 14 cases, respectively[601] While these organisms are usually saprophytic inhabitants of the intestine, the urinary tract, the pharynx, and the female genital tract, they are capable of producing diseases that were frequently fatal prior to the antibiotic era These disorders include bacteremia, meningitis, empyema, lung abscess, urinary and female genital tract infection, sinusitis, osteomyelitis, cervical sinuses, abdominal abscesses, otitis media, and thyroiditis Since the organisms (*B funduliformis* and *B fragilis*) have gas forming tendencies, they can also produce lesions simulating gas gangrene

Several bacteriologic considerations are sufficiently important to merit further comment Bacteroides bacilli are frequently associated with an aerobic or microaerophilic streptococci which may actually obscure the presence of the former Furthermore, unless adequate time for anaerobic growth is allowed and unless the subcultures are grown in Brewer's medium to which serum has been added, the bacilli are usually "lost"

THE SYSTEMIC MYCOSES

Histoplasmosis and Coccidioidomycosis

The systemic fungal infections are not rarities in temperate climes Although the manifestations of histoplasmosis and coccidioidomycosis are relatively well known, their systemic features bear repeated review in the evaluation of obscure febrile illnesses The histoplasmin and coccidioidin skin tests should, of course, be performed in the presence of persistent pulmonary lesions and thin walled cavities (p 124) This is particularly important if the tuberculin test is negative and if pulmonary and constitutional features are minimal The complement fixation studies have also been helpful (p 741) In certain instances, the periodic acid Schiff stain has greatly facilitated the recognition and study of the systemic mycoses[603]

It is emphasized that the incidence of dissemination of *coccidioidomycosis* to the skin, subcutaneous tissues, viscera, bones, and central nervous system is ten times greater in the dark skinned races than in caucasians This catastrophe is fatal in 50 per cent of those so affected In general, it is probably wisest to leave the asymptomatic cavity of pulmonary coccidioidomycosis alone inasmuch as there have been serious complications due to dissemination following surgery for this disorder Southern California, southern Arizona, and western Texas are recognized as the endemic areas of this disease in the United States The use of the aforementioned skin test and immunologic studies may be helpful in determining the probable existence of dissemination[604] (See Section VI in Part II) Attention is drawn to the greater frequency of this complication when erythema nodosum occurs It is also wise for clinicians to bear in mind the potential radiographic masking of coexisting diseases (particularly tuberculosis and bronchogenic carcinoma) by this disorder[436] There may be severe cardiac involvement in coccidioidomycosis, either due to a diffuse myocarditis or to a coccidioidal pericarditis with or without an effusion[60]

The cutaneous manifestations of coccidioidomycosis are depicted in Figure 84 (Atlas page 54)

from those caused by *Actinomyces israeli*, but the diagnosis can be made only by the isolation and identification of the organism Within the past two years, five cases of this disease have come to the author's attention from three thoracic surgeons In each of these patients, a pulmonary resection was performed for a presumed lung tumor

Mucormycosis

Mucormycosis is an entity that has begun to assert itself clinically during the past fifteen years It will undoubtedly command increasing attention by clinicians[500] In the cases reported in humans, *Rhizopus* rather than *Mucor* has been the pathogenic fungus Inasmuch as this ubiquitous organism is a common contaminant of cultures, it is necessary to demonstrate its presence in the sputum, the spinal fluid, or exudates for a definitive diagnosis

The unique feature of this fungus is its great affinity for spreading to blood vessels especially arteries with the production of a purulent arteritis and thrombosis after invading the muscular walls and lumina Another characteristic of this disease that is unusual among the mycoses is its rather acute course—most of the fatal cases occurring well within one month As noted in Group IV mucormycosis tends to affect specifically diabetics who are under poor control (p 141) Other predisposing influences include leukemia multiple myeloma fatal burns cirrhosis, and the use of cortisone, corticotropin the antileukemic chemical agents, and probably the antibiotics

This disease can manifest itself clinically in several manners The fungus may enter the nasal passages and create a sinusitis, an orbital cellulitis thrombosis of the ophthalmic and internal carotid arteries, an ophthalmoplegia and a meningoencephalitis In the pulmonary form, infection may be of a primary (bronchial) nature or of a hematogenous origin leading in turn to thromboses of the pulmonary vessels pulmonary infarcts and a lobular pneumonia Intestinal mucormycosis characterized by hemorrhagic and ulcerative lesions in the terminal ileum and large intestine and disseminated mucormycosis have also been reported[500]

Sporotrichosis

The majority of cases of sporotrichosis in this country are limited to the skin and the subcutaneous tissues The subacute or chronic course of the localized lymphangitic infection in which a series of subcutaneous nodules develop without a significant lymphadenopathy is rather characteristic The pathogenic organism *Sporotrichum schenckii*, was usually introduced several weeks previously following some minor trauma especially a scratch or prick with a sliver or a thorn The cutaneous lesions at times resemble those of actinomycosis but can be readily identified because of the rapid growth of the fungus on Sabouraud s glucose agar

Extracutaneous and hematogenous dissemination may take place In this instance, nodules in the skin are often present but the involvement is found over the entire body Systemic dissemination need not be accom

The cutaneous manifestations of North American blastomycosis are depicted in Figure 82 (Atlas page 52)

Actinomycosis

Actinomycosis may present itself in one of four clinical forms—cervicofacial, pulmonary, abdominal, and generalized Its clinical resemblance to tuberculosis has fooled almost every expert Similarly it simulates regional enteritis, lymphopathia venereum, and the other granulomatous or neoplastic diseases involving the intestine In regard to the so-called sulfur granule, Weed and Baggenstoss have correctly called attention to the fact that actinomycotic infections can persist for a long time without the formation of sulfur granules Furthermore, a variety of infections exclusive of actinomycosis may produce granules resembling those produced by the anaerobic actinomycetes, both grossly and in histologic sections [614] Only when typical filaments are demonstrated by the gram stain can the diagnosis be made Additional differential cultures are necessary from the therapeutic point of view, inasmuch as the so-called aerobic actinomycetes (now called *Nocardia*) are susceptible to the sulfonamides, while the anaerobic forms (now designated as *Actinomyces bovis* if of animal origin and *Actinomyces israeli* if of human origin) are susceptible to penicillin

The cutaneous manifestations of actinomycosis are depicted in Figure 83 (Atlas page 53)

It has become more apparent in recent years from reports by several clinics of large numbers of patients with actinomycosis that there is little correlation of this disease with age, race, sex, occupation or season These organisms normally inhabit the mucous membranes They may gain entrance into the deeper tissues through such breaks in the body membranes as dental extractions rupture of gastric or duodenal ulcers rupture of the appendix rupture of colonic diverticulae, perforation of the colon by fish bones, perforation of rectal abscesses and even through ascending urinary tract infections [614]

Furthermore, with the greater accuracy in clinical diagnosis and with the use of Brewer s thioglycollate medium for the detection of anaerobic organisms, the previously promulgated anatomic distribution of the primary sites has been altered considerably In their report of 37 cases, Harvey Cantrell and Fisher found the following distribution cervicofacial lesions 24 per cent, abdominal lesions 63 per cent, and thoracic lesions 13 per cent [614b] A gratifying cure rate in this disease can be achieved by a combination of long term penicillin therapy with wide excision of the infected tissues

Nocardiosis

Nocardiosis may be an acute or chronic infection, chiefly affecting the lungs or the brain It can closely resemble the suppurative manifestations of *Klebsiella, Pasteurella, Salmonella,* and *Malleomyces,* as well as the aforementioned mycotic diseases [615] The absence of extensive scarring, burrowing, or sinus formation serves to differentiate most of the nocardial lesions

Armed Forces Institute of Pathology, the diagnosis was correctly made in only 36 per cent[617] The incorrect diagnoses included carcinoma of the liver, ulcerative colitis, appendicitis, gastrointestinal malignancy, gallbladder disease, hepatitis pneumonia brucellosis, and nonspecific abscesses in the liver lung, or brain It was of added interest that there were 18 instances in which no detectable lesions in the intestine could be demonstrated Furthermore, hepatomegaly was found in a significant number of patients in whom neither large abscesses nor hepatitis" were present

In a review of the records of 1370 patients on whom complement fixation tests for amebiasis were performed at the National Institute of Allergy and Infectious Diseases the test was regarded as being especially valuable in the diagnosis of amebic liver involvement[618] The test was positive however in 17 5 per cent of cases with intestinal amebiasis It is hoped that the currently available complement fixation technique for amebiasis will be satisfactorily improved upon by some other such as that of the immobilization of *Entamoeba histolytica in vitro* by antiserum produced in the rabbit[618b] The availability of this type of test might also give a more accurate indication as to the true incidence of amebiasis due to pathogenic strains in the United States The present statistics of 5 to 10 per cent have always impressed the author as being quite out of line with the experience of most practising gastroenterologists In fact, they have probably contributed in a large measure to the significant number of patients now suffering from amebaphobia[1156]

The physician must be aware of the fact that certain amebicidal drugs can produce toxic reactions which might be mistaken for complications of the parasitic infection[619] One case in point concerns the *toxicity of carbarsone* This may be a result of either overdosage (i e, when given in exce s of 0 25 gm three times daily for more than ten days), hypersensitivity or the presence of arsanilic acid (not removed initially by the manufacturer or due to the hydrolysis of the arsenical preparation during storage) The manifestations of such toxicity include upper abdominal pain and tenderness, nausea, vomiting diarrhea an exfoliative dermatitis hepatic damage and central nervous system involvement

The presence of recurrent fever chills leukopenia splenomegaly, anemia and mild icterus are almost diagnostic of *malaria* in endemic areas Nevertheless both the unstained and stained blood smears should always be carefully examined for malarial parasites Daily or quotidian fever may be present if infection with several families of *Plasmodium vivax* has occurred, with maturation taking place on alternate days

Vague chronic symptoms after a satisfactory course of antimalarial therapy are commonly related to anxiety anemia and other noninfectious conditions Although malaria has been practically eradicated in the United States it may be encountered among drug addicts and others as a result of the use of communal needles and syringes Malaria must still be considered in veterans who have served in endemic areas even more than a decade ago[708] Recrudescence of a quiescent malaria is occasionally observed following surgical trauma or superimposed infection[497] The therapeutic diagnostic tests for both amebiasis and malaria are described in Section XIII of Part II (p 813)

panied by cutaneous lesions, however Involvement of the bones and joints constitutes the most frequent noncutaneous complication It may represent a periostitis secondary to the direct extension from the superficial lesions, or a synovial infection resulting from the hematogenous spread The lytic and destructive osseous lesions might be confused with both *metastatic malignancy* and *tuberculosis*, or with the other forms of infectious arthritis [613]

Other extracutaneous forms of the disease occur, but much less frequently than that which affects the skeletal system These include involvement of the buccal, pharyngeal and nasal mucous membranes, ocular involvement, "id reactions," and very *rarely involvement of the lungs*, the gastrointestinal tract, or the central nervous system The importance of establishing the diagnosis is enhanced by the relative specificity of iodide therapy Stilbamidine or 2 hydroxystilbamidine may also be of value

THE PARASITIC INFECTIONS

The recent wars have served to focus attention upon the parasitic diseases, particularly amebiasis and malaria While many others, such as kala azar and trypanosomiasis, do seriously affect multiple systems of the body, they are not considered here inasmuch as they are rarely encountered in North America The diagnostic difficulties associated with acute and chronic Chagas' heart disease will be discussed under Group IX (p 233)

Amebiasis and Malaria

As noted in the preceding chapter, the problem of *chronic amebic infection* with or without a hepatitis and liver abscess, may offer considerable difficulty in diagnosis (p 124) Even when repeated stool examinations fail to reveal the ova and parasites of *Entamoeba histolytica*, the possibility of amebic colitis as a cause of unexplained fever might be considered in certain instances in view of the readiness with which cure can be achieved [616b]

The pulmonary complications can be further subdivided into the following six categories (1) hematogenous pulmonary abscess without liver involvement, (2) hematogenous pulmonary abscess and independent liver abscess, (3) pulmonary abscess extending from a liver abscess, (4) bronchopulmonary fistula with little pulmonary involvement, (5) empyema extending from a liver abscess, and (6) pleural effusion without true pus [437]

It is well to carry out a careful search for *Entamoeba histolytica* in the stools when an unusual case of *intermittent intestinal* obstruction with an abdominal mass presents itself Of 119 patients with ameboma of the intestine who were reviewed by Radke 41 died, of these, only eight had received specific antiamebic therapy [616a] While combined treatment with atabrine and carbarsone frequently relieved the obstruction, this complication was first observed in several instances *during* antiamebic therapy

In another recent report of 148 fatal cases of amebiasis from the

visited foreign countries since World War II) [6,0] It appears that sanitation and hygiene are often more important in the causation of helminthiasis than climate *per se* Recent evidences of the considerations cited above are (1) the first case of American trypanosomiasis reported in the United States occurred in Texas in 1955, and (2) an outbreak of infestation with *Strongyloides stercoralis* took place in an institution and school in Illinois following the recent arrival of children from New Mexico

Trichinosis

Of the roundworm infestations trichinosis is still the most important by virtue of its incidence and potential seriousness It is always discouraging to note that statistics continue to affirm the fact that the incidence of trichinosis in the United States still apparently exceeds that in any other country [6,0] (The mere substitution of grain for raw garbage in feeding hogs could reduce the incidence of trichinosis in pork to about 0 05 per cent)

Trichinosis has masqueraded as rheumatoid arthritis, eosinophilic leukemia, typhoid fever meningitis rheumatic fever, dermatomyositis and periarteritis nodosa [6,21] Both severe hepatic and renal dysfunction may be encountered in trichinosis, as evidenced by marked bromsulfalein retention, hypoalbuminemia and all the stigmata of a fulminant acute or chronic glomerulonephritis [6] In fact portal cirrhosis portal hypertension, ascites and liver failure have even been noted The search for conjunctival petechiae and splinter hemorrhages under the nails can prove to be most rewarding The use of the corticoids and corticotropin following the early diagnosis of this disease has prevented prolonged morbidity and even death [6,3]

The cutaneous manifestations of trichinosis are depicted in Figures 32 and 87 (Atlas pages 21 and 56)

Ascariasis and Hookworm Infestation

In the presence of unexplained pneumonitis and eosinophilia (Loffler's syndrome) anemia, and gastrointestinal symptoms—particularly in the more tropical regions—the diagnoses of ascariasis and hookworm disease should be entertained [2,4] Intestinal ascaris infestation produces a significant mortality when obstruction volvulus strangulation perforation or peritonitis occur [6,5] Hepatitis, obstructive jaundice, and pancreatitis might also complicate the course of these patients as a result of the ductal invasion by the parasites The diagnostic and surgical considerations related to this type of intestinal obstruction will be discussed elsewhere (p 504)

Visceral Larva Migrans

Visceral larva migrans is an infrequently recognized disorder resulting from the ingestion of the embryonated ova of dog or cat roundworms (*Toxocara canis or Toxocara mystax*) It should be considered in patients with persistent and marked eosinophilia recurrent wheezing associated

Toxoplasmosis

"This disease is caused by the protozoan parasite, *Toxoplasma gondii*." Although it is generally regarded as a "rare bird" and as an infrequent cause of prolonged fever, toxoplasmosis does merit some attention by consultant physicians. The acquired infection in adults may be characterized by a maculopapular eruption (which tends to spare the scalp, palms, and soles), remittent fever, meningoencephalitis, myositis, arthralgia, myocarditis, bronchopneumonia, conjunctivitis, and lymphadenopathy.[634] While it can resemble the rickettsioses clinically, there is no response to the antibiotics. This disorder is being recognized with increasing frequency as the cause, in infants, of congenital encephalomyelitis with hydrocephalus, intracerebral calcifications, microcephaly, a characteristic chorioretinitis, and microphthalmus.

The diagnosis is made by the morbid changes produced in mice following the injection of blood or other suspected tissue into the brain or peritoneal cavity, and by the Sabin cytoplasm modifying test with dyes (p. 746). In an analysis of 107 cases of granulomatous choroiditis studied at the Wilmer Ophthalmological Institute between 1953 and 1955 with the skin and dye tests for toxoplasmosis, 37 patients (or 35 per cent) were attributed to this disease.[635] Very suggestive evidence has been obtained to indicate that one important pathway of human infection with *Toxoplasma* parallels that of trichinosis, i.e., the ingestion of undercooked pork coming from pigs (who are natural *Toxoplasma* carriers).[634b] On a regimen of pyrimethamine and triple sulfonamides, dramatic improvement has been observed in several patients with severe acquired toxoplasmosis.

Chorioretinitis and cerebral calcification in infants also occur in the entity known as cytomegalic inclusion disease, so that differentiation on clinical grounds may not be possible.[634c] In the latter condition, however, the dye tests and complement fixation tests for toxoplasmosis are negative. Furthermore, typical inclusion cells are found in the urine and gastric washings. Another cause of congenital nontoxoplasmic chorioretinitis is fetal mumps infection.[634d]

THE HELMINTHIC DISEASES

The consultant physician should be aware of the fact that a decided increase in the incidence of parasitic and "tropical" diseases has taken place in recent years in the United States—in large measure due to a redistribution of the helminthic disorders. The following circumstances are partly responsible for such a redistribution: (1) the migration of masses of people from the southern to the northern states, carrying with them *Ancylostoma duodenale* (hookworm), *Trichuris trichiura* (whipworm), and *Ascaris lumbricoides* (roundworm); (2) the entrance of thousands of working migrants from the West Indies and other endemic areas who lack proper hygienic instruction, carrying with them *Schistosoma mansoni* and other parasites, most notably *Wuchereria bancrofti*; and (3) the increase in air travel to endemic areas, as in the case of service and government personnel, missionaries, and tourists (two million American tourists have

of interest in this regard, however, that while three fourths of the 79 cases encountered at one large center since 1856 demonstrated cysts in the liver, distant organ involvement was uncommon when this particular organ was the site of the cystic process.[63c]

This disease presents somewhat of a paradox inasmuch as clinical familiarity with echinococcosis contrasts with the fewer than 1 per cent of practising physicians in North America who have actually ever encountered a case (due in large measure to the stability of the sheep population). For example only twelve instances of echinococcal cysts were uncovered in a review of the experience at the Massachusetts General Hospital over a twenty year period.[63] In contrast, the disease is not at all rare in South and Central America. It would appear that of the 538 cases of echinococcosis known to have occurred in this country, in only 38 could the infestation have been acquired in the United States.[632] By far the majority of the remaining cases were probably acquired in either Italy or Greece.

It will be recalled that man is an intermediary host in the cycle of this parasite. Echinococcosis may become clinically apparent in several fashions, such as the pressure of the cysts onto adjacent organs or their rupture into various structures (the bronchial tree, the biliary ducts, the digestive tract, the peritoneal cavity and skin), infection within the cysts, or metastases of the cysts.[63] There is a much rarer alveolar form of the disease in which the organs are invaded by an expanding network of alveoli without the chitinous outer wall (presumably due to *E. multilocularis* rather than to *E. granulosus*). Calcification of the cysts is usually a function of the maturity of the lesions as well as their size, but its presence does not necessarily indicate the death of the cysts. The skin and serologic tests for echinococcosis are discussed in Part II (p. 748).

CYSTICERCOSIS CEREBRI

The discussion of tapeworm infestation will be limited to the problem of cysticercosis cerebri, in which the brain is infected with the larval form of the pork tapeworm (*Taenia solium*). It is recalled that while man is the definitive host for this parasite the eggs of the adult worm may be ingested by him either as a result of the fecal contamination of his food or from autoreinfection by the regurgitation of the ova. The embryos are subsequently disseminated via the blood stream.

This entity has assumed increasing significance in neurosurgical centers—even in this country—since intracranial cysts are reported in from 40 to 82 per cent of cases of human cysticercosis (p. 368).[633] The cerebral involvement can be one of three types: (1) solitary or multiple cysts, giving evidence of an expanding intracranial mass lesion; (2) widespread infection of the brain without localizing signs particularly in children; and (3) hydrocephalus resulting from the proliferative inflammatory reaction incited in the basilar meninges. It is apparent that a wide variety of central nervous system disorders might be simulated, such as brain tumors (especially mid line neoplasms in the posterior fossa), epilepsy, pseudotumor cerebri (meningeal hydrops), Alzheimer's or Pick's disease, and syphilitic meningitis.

with pulmonary infiltration hepatosplenomegaly of undetermined nature, hypergammaglobulinemia, and ocular disorders or central nervous system disturbances (including convulsions) of obscure etiology [6 4] Since this infection usually occurs in young children as the result of pica, the disease may also be associated with ascariasis or even plumbism

This diagnosis is more difficult to make than that of *Ascaris lumbricoides* since the larvae of *Toxocara* usually do not complete their life cycle in man Consequently, they do not reach the egg laying stage in the human intestine [6 4b] They are nevertheless capable of invading the viscera, in which case survival for several months is possible

Schistosomiasis

Schistosomiasis must be thought of when a chronic illness with hepatomegaly portal hypertension fever, splenomegaly, and eosinophilia affects men who have served with the armed forces in Japan, China Korea, Egypt, the Philippines, and especially in Puerto Rico [626, 627a] It is estimated that 20 to 25 per cent of the population in Puerto Rico harbor this parasite [626] The rectal biopsy and liver biopsy techniques are relatively simple and have proved to be most rewarding in diagnosing infection due to *S mansoni* and *S japonicum* (pp 795 and 798) [628, 629] Chronic urinary bladder ulceration and metaplasia are features of vesical schistosomiasis (due to *S haematobium*) The widespread nature and implications of this disease, particularly as they relate to involvement of the central nervous system, have been recently emphasized by reports stemming from such unusual sources as insurance examiners and neurosurgeons [630]

After a variable incubation period[630] (in which cutaneous lesions are infrequent), *acute Manson s schistosomiasis* exhibits an explosive onset with severe constitutional manifestations that may be indistinguishable from those of typhoid fever and other acute infections The clinical picture is dominated by gastrointestinal, hepatic, and pulmonary dysfunction along with evidence of a severe hypersensitivity state (hypereosinophilia, Loffler's syndrome) when full maturation of the parasite and oviposition have occurred [631] Hyperglobulinemia hepatomegaly, splenomegaly a generalized lymphadenopathy, and profound alterations in liver function are almost universally encountered In this early phase of infestation due to *S mansoni* the stool examination for the eggs of the parasite is more apt to be rewarding than serial rectal biopsy specimens Furthermore in this stage of the infestation, the prompt administration of stibophen (Fuadin) can affect a transitory or prolonged suppression of oviposition

Echinococcosis

The more impressive clinical and surgical aspects of echinococcosis in the presence of hydatid cystic disease of multiple organs are well known When an abdominal echinococcus cyst is suspected, the importance of chest films and x rays of other parts of the body is pointed out by the fact that 60 per cent of patients with hydatid disease prove to have cysts elsewhere in their bodies, with pulmonary lesions occurring in 21 per cent [63 b] It is

infection may be associated with a general lymphadenopathy, an extensive erythematous or macular eruption, arthritis periostitis perichondritis, conjunctivitis, epididymitis, nephritis, and very frequently a positive Wasser mann test [638] There is usually a prompt response to the arsenicals, and often to penicillin

' Haverhill fever" due to infection by *S moniliformis* is characterized by a morbilliform eruption (particularly over the extensor sides of the extremities) with a tendency to purpura, a bacteremia (with or without an endocarditis) severe headache subcutaneous abscesses, bronchopneumonia and a polyarthritis [639] [640] The last often accompanies the second bout of fever one week after the onset of the infection The incubation period in this disease is only three to seven days in contrast to the several weeks when the infection is due to *S minus* It may also follow the ingestion of contaminated milk The growth of the organism from the patient s blood or joint fluid (in tryptose phosphate and dextrose starch with added ascitic fluid or animal serum) and the rising agglutination titers confirm the diagnosis Penicillin is usually curative

Relapsing fever due to *Borrelia recurrentis* has been recognized in this country only in Texas and west of the Rocky Mountains It is spread principally either by ticks or by the body louse under conditions of poverty and close crowding In addition to the fever and toxicity, muscle tenderness (particularly in the calves) an interstitial myocarditis intracranial hemor rhage a transitory erythematous or petechial eruption and enlargement of the spleen with abscess formation may be noted Jaundice is infrequent The organism can readily be recovered from the peripheral blood during this stage

Not only do most patients develop agglutinins for Proteus OX K in this di ease but a significant number also demonstrate false-positive serologic tests for syphilis [641] It is of interest that in a recent report of 11 fatal cases due to louse borne relapsing fever six patients had a coexistent infection with either *Salmonella* or *Shigella* [642]

CAT SCRATCH DISEASE

This disorder has been recognized with increasing frequency in the past decade and is usually self limited, benign, and readily diagnosed The skin test and its evaluation are discussed in Section VI of Part II (p 748) The development of the primary lesion at the site of a scratch by a cat thorn, or other object—followed by days or even weeks before the onset of the regional lymphadenopathy (without an associated lym phangitis) and fever—is classic (Cats transfer the presumed virus from their mouth and nasal passages in the act of washing)

Attention is directed to several variants and potential sources of con fusion [643] Erythema nodosum has been reported with this disease A mesenteric lymphadenopathy is also described in which the histologic features were compatible with cat scratch disease Similarly reference is made to a probable thoracic form of this disease manifested as a mediastinal lymphadenopathy and pneumonia A number of instances in which the typical lesions were accompanied by convulsions, encephalitis and other

The presence of the aforementioned features in individuals who have resided for long periods in such countries as Mexico, Chile, and Spain renders this diagnosis a strong possibility This is particularly true when these symptoms are associated with multiple small areas of calcification, an eosinophilia of the blood and spinal fluid, and a positive complement fixation test of the spinal fluid to an alcoholic extract of porcine cysticerci (p 742)[63 b]

LEPROSY

A few words concerning leprosy are justified because an occasional case turns up either indigenously or in travelers and service personnel returning after prolonged sojourns to the tropical climes[636] In a review of 1465 patients (822 being American born) who were admitted to the National Leprosarium at Carville, Louisiana since its opening in 1921, at least one patient was admitted from each of forty states, most notably from certain sections of New York, Florida, Louisiana, Texas, and California[636b] The administration of the effective therapy now available can halt the progression of this once dreaded illness, provided it is diagnosed early

It will suffice to recall that the peripheral nerves and skin are primarily involved This results in the enlargement of the peripheral nerves, the cutaneous lesions and the superficial tactile and thermal anesthesia The anesthesia is frequently misdiagnosed as either syringomyelia or multiple sclerosis The lymph nodes spleen, and bone marrow may also be invaded[637] The presence of persistent proteinuria and hepatosplenomegaly in leprosy is highly suggestive of secondary amyloidosis In fact, this complication can occur in relatively young people who have had the disease only a few years, and represents the leading cause of death from lepromatous leprosy in this country[200]

Skin biopsy is almost mandatory in nonendemic areas, since mycosis fungoides and other nodulogenic tumors can produce clinical pictures that closely mimic leprosy The dermatologic pattern may also resemble psoriasis, tinea circinata urticaria, and other common dermatoses The dermadromes include a diffuse granulomatous infiltration with macules papules, and even nodules in the lepromatous type (representing 85 per cent of indigenous cases in the continental United States), or erythematous and often papulated macules in the tuberculoid type In the latter variety, anesthesia is almost invariably present and the patient reacts to lepromin (p 749)

RAT BITE FEVER AND RELAPSING FEVER

"*Rat bite fever*" is a general term describing infection by either the *Spirillum minus* or *Streptobacillus moniliformis* organisms As in one case with which the author is familiar, merely asking the patient if she had been bitten by a rat or mouse resolved the cause of an otherwise puzzling acute severe polyarthritis

In addition to the relapsing fever and the lymphangitis, *S minus*

GROUP VI

Hematologic Diseases

THE LEUKEMIAS

THE LYMPHOMAS

LIPOMELANIC RETICULOSIS

MULTIPLE MYELOMA

HYPERGLOBULINEMIA

MACROGLOBULINEMIA

POLYCYTHEMIA VERA
Relative polycythemia Secondary polycythemia

GENERAL CONSIDERATIONS IN THE EVALUATION OF OBSCURE ANEMIAS

PERNICIOUS ANEMIA
Differential diagnosis of macrocytic anemias Combined system disease

THE HEMOLYTIC ANEMIAS
Congenital Acquired

ERYTHROBLASTOSIS FETALIS

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

IDIOPATHIC PAROXYSMAL MYOGLOBINURIA
'Exercise myohemoglobinuria

SICKLE CELL ANEMIA AND ITS VARIANTS

HEREDITARY LEPTOCYTOSIS

FAVISM

INFECTIOUS MONONUCLEOSIS

SPLENOMEGALY—DIFFERENTIAL DIAGNOSIS

MYELOID METAPLASIA

FOR AUTHORITATIVE definitions of current nomenclature and a classification of the various hematopoietic abnormalities as devised and ac

central nervous system features are also on record [644] One final comment relates to the difficulties the pathologist is apt to encounter, since the histologic picture of "feline lymphogranuloma" is for all practical purposes identical with that of lymphogranuloma venereum This issue is further complicated by the fact that a positive complement fixation reaction to the lymphogranuloma antigen occurs in these patients (p 744) [643b]

the manner with which each individual patient handles his particular disease Generally speaking it is true that reticulum cell sarcoma is apt to differ from lymphosarcoma clinically in its peak incidence among the older decades, its tendency to involve bone, and the rarity of leukemic changes in the blood Nevertheless, one must constantly bear in mind that students of this group of diseases repeatedly caution against making dogmatic diagnoses or prognoses on the basis of such individual features[649] As a rule the occurrence prior to therapy of leukopenia skin infiltration and moderate anemia are usually poor prognostic signs in Hodgkin s disease

Persistent pruritus symptomatic herpes zoster (either localized or generalized and particularly with hemorrhagic necrotic or bullous components), and eruptions or infiltrations of all possible types are common early *cutaneous manifestations* of the leukemias and lymphomas—even before an adenopathy is detectable (p 538)[516 650] In this regard it should be noted that mycosis fungoides has not infrequently misled experienced dermatologists by its ability to simulate psoriasis parapsoriasis pityriasis rosea, poikiloderma vasculare atrophicans, other types of exfoliative dermatitis and even leprosy Poikiloderma vasculare atrophicans may remain as a distinct entity or it may be transformed into one of the lymphomas or leukemias Pruriginous lesions are often noted in Hodgkin s disease, along with the bleeding and infected papules that result from the extensive scratching caused by the intense pruritus Reference has been made previously to the nontender presternal edema associated with the interference of the lymph drainage of the anterior chest wall by the sternal and retrosternal involvement (p 158)[570b]

The diffuse melanoderma sometimes observed in Hodgkin s disease can be so extensive as to simulate adrenocortical insufficiency On occasion a widespread diffuse bright red to dusky erythroderma (l homme rouge) may antedate the hematologic diagnosis of leukemia The pigment of chloroma may be seen about the face and head in various leukemias usually the myelogenous type in children An ichthyosiform atrophy of the senile-ichthyosis type has been the principal presenting feature of Hodgkin s disease Although the peculiar dryness of the skin becomes increasingly apparent with progression of the disease this condition has exhibited repeated and remarkable remissions following x ray and nitrogen mustard therapy[650] The close relationship of these various diseases is again pointed out by the fact that a patient may have an apparent case of mycosis fungoides clinically yet the blood smear may be that of leukemia while the pathologic diagnosis of an excised lymph node is consistent with lymphosarcoma[651] It has been estimated that up to one half of cases of exfoliative dermatitis beginning in the later decades of life ultimately prove to be lymphoblastomatous in origin[651]

Several of the dermadromes of leukemia and Hodgkin s disease are depicted in Figures 18 25 and 26 (Atlas pages 11 16 and 17)

Central nervous system lesions or symptoms (as compression of the spinal cord by extension into the epidural space or the collapse of a vertebra) infiltration or compression of any part of the gastrointestinal tract, pulmonary infection oral sepsis chronic sore throat bone tenderness, and rheumatoid or neuritic discomforts may be the presenting complaints in

cepted by leading hematologists, the reader is referred to the report of the Committee for the Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood Forming Organs[645] The listing and analysis in Section I of Part II (Hematologic Studies) has been presented as an aid in the diagnosis of the manifold variations of these hematologic syndromes

It is apparent that in the presence of any combination of pallor, anemia, bleeding, lymphadenopathy, splenomegaly, and significant leukopenia or leukocytosis should direct one's attention to primary disorders of the hematopoietic system I am continually impressed by the silent and compensated manner in which these diseases can remain dormant for long periods of time, and how closely they may on occasion either mask or accompany one another or other diseases For example, thrombocytopenic purpura has been the initial manifestation in a variety of hematopoietic disorders (leukemia, lymphoma, aplastic and myelophthisic anemias, infectious mononucleosis, myeloma) It may also be a prominent feature in a number of other diseases, including tuberculosis, lupus erythematosus, sarcoidosis, Gaucher's disease, and subacute bacterial endocarditis Another striking instance in which a prolonged "silent" phase is commonly encountered is that of chronic lymphatic leukemia Even when an adenopathy and anemia cannot be found, the presence of a marrow lymphocytosis exceeding 20 per cent and an absolute lymphocytosis in the peripheral blood persisting for months is highly suggestive of this disorder[646]

THE LEUKEMIAS AND LYMPHOMAS

The leukemias and lymphomas are prime examples of the aforementioned phenomenon of diagnostic evasiveness, and merit considerable emphasis in this text By way of review, the usual pathologic connotations of the term 'lymphoma include lymphosarcoma, reticulum cell sarcoma, follicular lymphoma Hodgkin s disease (paragranuloma, granuloma sarcoma) mycosis fungoides Spiegler Fendt sarcoid, mixed types, and in some quarters myeloma and erythrocytic sarcoma Inasmuch as there are several systems of classification, it is most important for the clinician to know which one is being used by a particular pathologist[647a]

Transitional clinical and morphologic forms between the various lymphatic tumors (malignant lymphoma and lymphatic leukemia) and the plasmacytomas are occasionally found These occur in those occasional patients with the former diseases who are found to have either abnormal serum proteins characteristic of multiple myeloma, or a marked plasmacytosis or a large number of pyroninophilic reticulum cells and lymphoid cells in tissue sections or in bone marrow aspirations[647b]

Similarly, in a comprehensive re evaluation of the status of follicular lymphoma, Rappaport Winter and Hicks have clearly shown the tendency of malignant lymphomas with a follicular pattern to progress into diffuse lymphomas usually of the corresponding cell type[648] The so called Hodgkin's paragranuloma described by Jackson and Parker is quite infrequent in its classic form It probably represents a relatively benign and slowly evolving transitional phase of Hodgkin's disease[648b]

The authorities in this field have emphasized the wide differences in

velop amyloidosis, as is usually manifested by proteinuria and azotemia[198]

Contrary to some teachings, there is a wide variation in the consistency of the nodes in Hodgkin's disease The history of severe pain being promptly induced by the ingestion of wine, beer or other alcoholic drinks should alert the physician to the diagnosis of this disease[659] It is of interest that most patients will experience a remission of this phenomenon following nitrogen mustard or irradiation therapy Unfortunately, alcohol induced pain has also been observed in several patients suffering from carcinoma and other cancers (pancreatic, thymic)[659c]

Radiographic changes in the bones are infrequent in adults with leukemia, but they may appear as a diffuse increase in density The reverse holds true in the case of children The findings here can vary from such minimal abnormalities as transverse bands of decalcification at the metaphyses to diffuse calcification, gross areas of destruction, and widespread periosteal proliferation[657] The occasional instances of striking hypercalcemia in Hodgkin's disease, along with the increased susceptibility of these patients to the toxic effects of vitamin D, have been alluded to previously (p 82)[816]

It should be emphasized that all possible combinations of anemia, leukopenia and thrombocytopenia can precede the clinically recognizable phase of leukemia by as long as two years in spite of the most careful and repeated hematologic study This must always be borne in mind before diagnosing a case as 'primary splenic panhematopenia' or 'primary aplastic anemia'[661] The clinician must also be cognizant of the fact that hypersplenism is occasionally an important complicating factor in chronic lymphocytic leukemia or malignant lymphoma[66] If it can be shown that the red blood cells are being destroyed at an abnormally rapid rate, or if there is a thrombocytopenia or granulocytopenia in the presence of a marrow that appears capable of producing these blood constituents in adequate numbers, splenectomy might produce a significant salutory effect An autoimmune hemolytic mechanism is particularly common in chronic lymphocytic leukemia The importance of not confusing myeloid metaplasia, aplastic anemia due to other causes, and leukemoid reactions with leukemia is apparent Specific reference is made of the ability of hematogenous tuberculosis to simulate the acute and subacute leukemic states both clinically and hematologically[533b, c] In view of the available specific antimicrobial therapy that can be curative (if administered in time) and the frequency with which the misdiagnosis recurs in practice and at clinicopathologic conferences, this situation must be constantly kept in mind by clinicians, especially hematologists Attention is directed to the fact that the bone marrow can be essentially normal until the terminal state in cases of leukemia where the site of origin is in the liver spleen or other extramedullary organs[661]

One must be particularly wary of the possibility of leukemia or lymphoma in every patient with a vague hematologic syndrome who has previously been exposed to significant amounts of diagnostic therapeutic occupational (radar), or military radiation[663, 1168, 1169, 1195] This orientation is especially germane in the case of patients with polycythemia vera who have received either x radiation or P^{32} therapy and then do poorly

the leukemias or lymphomas.[69, 95, 96, 514, 515, 654, 655] The possibility of lymphosarcoma should be entertained in the presence of a neoplasm that is associated with an increased, rather than a decreased, calibre of the bowel lumen.

It is not unusual for acute leukemias in children to simulate severe acute infections or the *exanthematous diseases*.[657b] *While febrile episodes* commonly occur in leukemia and are usually regarded as characteristic of the disease itself, one should not overlook the possibility of an underlying bacteremia (but not necessarily a septicemia or an abscess). This was clearly pointed out by the fact that positive blood cultures (usually with staphylococci, *Pseudomonas*, or colon bacilli) were obtained during 38 of 42 bouts of fever in a group of 41 leukemic patients.[657c]

The association of the lymphomatous diseases with fungal infections, even in the absence of antibiotic or steroid therapy, is not limited to torulosis,[608, 609] but may include histoplasmosis and others.[607] It used to be said that "tuberculosis follows Hodgkin's disease like a shadow." In fact, an incidence of 20 per cent was encountered in some of the early studies by Parker and Jackson.[635d] This association may be related in part to the relatively longer periods of survival in the lymphomatous patients, and in part to the defective immune mechanism in both the production and the transport of cellular antibodies that exists in Hodgkin's disease.[652] Where the possibility of a coexisting or pre-existing tuberculous process arises in a lymphomatous patient who is being considered for steroid therapy, the clinician should seriously consider the prophylactic use of INH. On the other hand, Hodgkin's disease and bronchogenic carcinoma occasionally will arise *de novo* in the patient with active or inactive pulmonary tuberculosis.[635c]

In acute leukemia, *neurologic involvement* occurs in from 25 to 50 per cent of the cases, and may first present itself after a peripheral blood and bone marrow remission has been achieved with antileukemic therapy. Since retinal hemorrhages are often present in these patients, the finding of a *subhyaloid hemorrhage is helpful in diagnosing the frequent* complication of intracranial hemorrhage.[48] Although invasion of the brain substance itself by Hodgkin's granuloma is presumed to be rare, the courses of several patients with weakness, tremors, speech difficulties, and repeated generalized convulsions have been carefully documented, along with ensuing dramatic remissions following nitrogen mustard therapy.[658] When no compression is evident, spinal cord lesions (particularly in the midthoracic region) may be due to occlusion of the segmental arterial supply to the spinal cord by these retroperitoneal or posterior mediastinal tumors—provided a radiation myelitis is excluded.[654] A polyneuropathy similar to that seen with carcinoma and myeloma is also observed in lymphoma and leukemia.

Renal involvement, as evidenced by albuminuria, hematuria, and casts, may be the first manifestation of Hodgkin's disease and lymphosarcoma. Hypertension, azotemia, and even the nephrotic syndrome later become apparent.[130] In this regard, it is well to recall that patients with Hodgkin's disease who survive for prolonged periods of time following the administration of several courses of nitrogen mustard therapy are prone to de-

LIPOMELANIC RETICULOSIS

The entity of lipomelanic reticulosis deserves internists dermatologists and pathologists alike ma… a benign process that is usually confused with Hodgk… lymphoblastomas and exfoliative dermatitis of differ… drome is characterized by a chronic pruritic dermatos… lymph nodes, generalized pigmentation or depigme… philia [870] The disorganized lymph node structure is ac… plasia of the reticulum cells, eosinophilia, and the pre… melanin and lipoid material—all of which contribute… fusion In fact these patients are not infrequently… melanocarcinoma

MULTIPLE MYELOMA, HYPERGLOBULIN… RELATED DISORDERS

Although the disease was considered somewhat… years ago my association with several colleagues who… in the problem of *multiple myeloma* has amply dem… not the case *if* the disease is kept in mind Since th… sionally be successfully treated any patient over for… a male) with unexplained anemia azotemia persiste… porosis, recurrent pneumonia Raynaud s phenomen… po ure to cold proteinuria or an anti complementa… should have further bone marrow blood protein, and… pressive instances of familial myeloma are on record

In both myeloma and lymphoma striking man… associated amyloido is may be present in the hear… glands One out of five patients with myeloma is foun… enlarged liver or spleen On the other hand significa… and hemolytic anemia are only infrequently encou… features of myeloma Although quite rare there are… well documented concomitant Paget s disease of th… myeloma on record, so that this particular dual di… should there be specific indications for the coexistence…

A series of six patients with myeloma has bee… evidence of an atrophic areflexic, motor sensory pol… initial or most striking clinical manifestation [a b] Th… ilar to that seen in association with carcinoma (p… pre sive lesions affecting the central nervous system… form of spinal cord involvement and compression,… present as acute paralysis of the lower limbs This… pressure exerted by an extramedullary tumor, a coll…

One should also consider leukemia or lymphoma in individuals whose siblings have been afflicted with either of these disorders [664] In one study of 110 verified cases of Hodgkin's disease, 15 families were encountered in which proved multiple cases of either this disorder or another of the lymphomatous diseases developed in blood relatives [664f] There may also be a relationship between mongolism and acute leukemia (possibly based on the damage to both the germ cells and the bone marrow in the sixth to ninth week of embryonic life), as indicated by the significant frequency of this combination [664e] Note is made of the relative frequency with which an independent focal malignancy has complicated the course of patients with either leukemia or lymphoma, especially when the last two are of prolonged duration [1011]

The alteration in the natural course of the acute leukemias (and to a lesser extent the chronic leukemias and myeloma) by the antibiotics, the chemotherapeutic agents, ACTH, and the adrenocortical steroids has also introduced several *complications of therapy* These are related both to the prolonged survival of such patients and to the effects of these drugs Particularly noteworthy is the invasion by pathogenic and antibiotic resistant bacteria and by the "opportunistic fungi," most notably so in the case of cerebral and pulmonary mucormycosis [811, 812]

The potential deleterious effects from the *hyperuricemia* associated with the treatment of both the acute and chronic leukemias and lymphomas should be considered in the management of these patients Very high ele- mulions of the uric acid may follow therapy with the steroids, nitrogen This'rd 6-mercaptopurine, methotrexate (Amethopterin), and radiation or pre-particularly likely when leukemic infiltrations within the kidneys ent [183] A sting renal damage and hyperuricemia are concomitantly pres constitute renal failure or acute ureteral obstruction by uric acid stones induced hype most significant complications of such a therapeutically ing of fluids aricemia They might be obviated by the prophylactic forc

On several he oral administration of alkali the author as provisions, *retroperitoneal lymphoma* has presented it *elf to* in whom no speci d fever sweats, weakness, and weight loss in patients study That this is i gnostic clue could be found, even after *intensive* quency with which thi uncommon situation is evidenced by *the fre-* ences [665, 666] The syndrom sideration recurs at clinicopathologic confer subsequent anuria or uremi unexplained ill health, anemia backache, and turbances—has been reportec the absence of any preceding urinary dis- to retroperitoneal tumors or re ases of bilateral ureteral obstruction due have resulted in *periureteric fi* ritoneal inflammatory processes which diagnostic remission with adequ [667, 668] Under these circumstances a to be most helpful Obliteration nounts of nitrogen mustard can prove in the author s experience The e psoas shadow has been infrequent itoneal pneumography has also be vely simple technique of retroper of these neoplasms [669] If the aforen uccessful adjunct in the diagnosis exploratory laparotomy may be the ed studies are still equivocal, an achieving a diagnosis *prompt* and definitive means of

The cases described by Waldenstrom and others as *"purpura hyper globulinemica"* may well prove to be variants of sarcoidosis, systemic lupus erythematosus, or the lymphomas [676] In the cases that are on record, it has been predominantly encountered in females after puberty who demonstrate transient crops of petechiae or a purpuric eruption usually on the lower extremities Some difficulty may be experienced in differentiating the morphea of this eruption from the progressive pigmentary dermatoses of Schamberg and Majocchi (pp 225 and 520), and to a much lesser degree with the allergic purpuras the thrombocytopenic purpuras, and disseminated lupus erythematosus

While hepatosplenomegaly, a moderate generalized lymphadenopathy, limb tenderness and an anemia have accompanied the elevated gamma globulin—particularly in the secondary type—it is usually encountered as a benign disorder with few striking findings in the so-called primary form Nevertheless prolonged observation of patients with purpura hyperglobulinemica is obviously necessary since the dysproteinemia, the marrow lymphocytosis, and the anemia may represent the "silent phase" precursors to an ultimate myeloma Such, in fact, was the outcome in one recently reported patient who had this condition for ten years previously [676c]

MACROGLOBULINEMIA

The syndrome of macroglobulinemia as also originally described by Waldenstrom has been reported with sufficient regularity to merit its inclusion in this text [677, 678] It is predominantly an affliction of males over the age of fifty, and is characterized by weakness weight loss, pallor frequent nasal and oral hemorrhages and occasionally subarachnoid or ocular hemorrhages Mild painless lymphadenopathy hepatomegaly and splenomegaly are frequently present Examination of the blood reveals an anemia but usually normal white blood cell and platelet counts, and normal bleeding and coagulation times There is also a hyperglobulinemia a markedly elevated sedimentation rate, demonstrable euglobulins and spontaneous gelification of the serum on cooling The bone marrow may present a confusing morphology with a striking increase in unusual mononuclear cells Neither the bone marrow changes nor the skeletal defects of myeloma chronic lymphatic leukemia, or lymphosarcoma are found however, notwithstanding the feeling of some authors that macroglobulinemia represents a rare variant of these diseases It is possible that macroglobulinemia may be subsequently shown to actually represent a specific lymphomatous disorder

The demonstration of *macromolecules* by ultracentrifugation (single or multiple high molecular weight proteins sedimenting in significant concentrations with Svedberg constants of more than 15S) is insisted upon by most authorities in establishing this diagnosis By electrophoresis the globulin macromolecules may be found in the gamma beta, and zeta zones, indicating the multiplicity of underlying defects in protein synthesis Although they are not homogeneous by ultracentrifugation, the macroglobulins appear to be antigenically pure An excellent review of this subject and its relationship to cryoglobulinemia has been presented by Mackay

absence of isoagglutinins they may encounter While myeloma cells are found only rarely in the peripheral blood of these patients, the abnormal plasma proteins effect certain changes in the peripheral blood which should always be recorded by the trained laboratory technician These include marked rouleau formation, "greasiness," a peculiar dark blue coloration of the stained smear, and the very rapid sedimentation rate [672a] The finding of Bence-Jones proteinuria is associated with significant renal insufficiency in one half of these patients, and is usually a poor prognostic sign

The negativity of one or two bone marrow reports *cannot* be considered as absolute evidence against a diagnosis of multiple myeloma It should be emphasized that plasmacytosis of the bone marrow (a minimal of 5 per cent plasma cells) may also be due to many conditions other than myeloma (p 675) [673] Attention was directed earlier in this chapter to the existence of transitional clinical and morphologic types between the various tumors of lymphatic origin and the plasmacytomas (p 180) The separation of the serum proteins by the relatively simple paper electrophoretic technique has proved to be eminently satisfactory in detecting the hypergammaglobulinemia (p 692) [674] The subject of cryoglobulinemia is discussed further in Group VIII (p 220)

The diagnostic implications and clinical value of *hyperglobulinemia* continually confront the diagnostician in evaluating difficult clinical case material On a number of occasions, myeloma, sarcoidosis, and the dy collagenoses have been initially suspected on the basis of this finding It has been shown that serum globulin values of 5 0 gm per 100 ml or higher are of considerable diagnostic import, particularly for these three types of disorders [675] Moreover, further diagnostic study for a wide variety of diseases in the group with intermediate elevations (4 0 to 5 0 gm per 100 ml) may also prove to be quite fruitful

In patients without overt liver disease, the thymol reaction appears to be a very sensitive indicator of serum globulin elevations, particularly as they are related to increases in the gamma globulin fraction No correlation between the height of the serum globulin and the alkaline phosphatase, the BSP retention, or the incidence of false-positive serologic tests can usually be found Certain technical features bearing upon the evaluation of elevated serum globulins are reviewed in Section II of Part II (p 692)

It would be well to briefly elaborate upon the "specific hyperglobulinemic diseases ' The following listing is a modification of the one recently presented by Feinstein and Petersdorf in their review of this subject [675]

Laennec s cirrhosis
Other liver disease
Nonmetastatic carcinoma
Metastatic carcinoma
Multiple myeloma
Lymphomas
Collagen diseases
 Acute rheumatic fever
 Acute glomerulonephritis
 Systemic lupus erythematosus
 Rheumatoid arthritis
 Periarteritis nodosa
 Scleroderma

Sarcoidosis
Chronic pulmonary disease
Infectious diseases
 Lymphogranuloma venereum
 Subacute bacterial endocarditis
 Syphilis
 Trichinosis
 Tuberculosis
 Schistosomiasis
 Kala azar
 Brucellosis
Macroglobulinemia

resulting from marked obesity and the concomitant alveolar hypoventilation.[143,150] That this polycythemia is not of the primary type is shown by the absence of leukocytosis, thrombocytosis, myeloid immaturity and splenomegaly, the presence of arterial hypoxemia and the disappearance of this abnormality following weight reduction without other therapy.

A few instances have been reported in which a significant polycythemia was associated with hypernephromas or other renal tumors[685] and with uterine fibromyomas.[686] In both instances the polycythemia quickly disappeared following either nephrectomy or hysterectomy. Here again, the abdominal tumors may have restricted the ventilatory capacity, producing alveolar hypoventilation, but this would not appear to completely explain the phenomenon. A relative polycythemia is not uncommonly seen in patients suffering from increased intracranial pressure. Similarly polycythemia due to an induced erythrocytosis is also described in conjunction with certain subtentorial tumors, most notably cerebellar hemangioendotheliomas and solid hemangioblastomas.[687] The finding of polycythemia and numerous Howell Jolly bodies in an infant with serious congenital heart disease is almost pathognomonic of congenital asplenia.[524]

OBSCURE ANEMIAS

The anemias are discussed briefly inasmuch as the hematologic findings, particularly the carefully studied peripheral blood and bone marrow smears, are usually diagnostic. Since these are often omitted and since practically every patient seen in consultation for an anemia has already received "shotgun" hematinic treatment, one must constantly fall back upon the basic hematologic principles and techniques.

The importance of seeking lesions that are causing chronic blood loss (particularly hiatal hernia) cannot be overstressed when confronted with the so-called refractory anemias. Even in the unusual cases where all the features of the Plummer Vinson syndrome (smooth tongue, iron deficiency type of anemia, dysphagia and webs in the cervical esophagus or below the level of the cricopharyngeus muscle) are encountered, a careful search for a complicating gastrointestinal malignancy is in order. The same emphasis also applies to a number of other treatable conditions which commonly present themselves in the form of undiagnosed anemias. These include hypothyroidism (p 16),[27] subacute bacterial endocarditis (p 114),[405] azotemia (p 50)[679] and vitamin D intoxication (p 403).[182] A peculiar blood picture in the presence of congenital heart disease—particularly with the finding of Howell Jolly and Heinz bodies in more than 10 per cent of the circulating erythrocytes, target cells, decreased osmotic fragility, siderocytosis and leukocytosis—may be due to an associated agenesis of the spleen rather than to an endocarditis (p 426).[524]

A chronic hypoplastic anemia stemming from a hypoplastic process affecting only the erythrocytic (but not the myelocytic or megakaryocytic) elements of the bone marrow is quite uncommon, and is encountered primarily in children. When confronted with a chronic normocytic normochromic or macrocytic normochromic anemia in the presence of infrequent reticulocytes, normal white blood cell total and differential counts, normal

and his colleagues[678] A simple screening "bedside test" advocated for this disorder consists in the placing of one or two drops of serum into distilled water It has been suggested that if a white precipitation ensues, macroglobulins may be present, and further corroborative studies are indicated (p 681)

POLYCYTHEMIA AND RELATED DISORDERS

Polycythemia vera can usually be readily diagnosed merely by inspection of the patient Not infrequently however, the patient presents himself with cerebral symptoms referable to the increased blood viscosity (headache, tinnitus, dizziness, and mental changes) These are often misdiagnosed as neurasthenia The decalcification of the vertebrae may become so marked in polycythemia as to lead to spontaneous fractures Dameshek has noted that one third of these patients will experience intense pruritus after a bath, a phenomenon which differs from the pruritus described by patients with lymphoma[680] The facial erythema accompanied by pruritic papules is not infrequently initially diagnosed as rosacea

At other times, a complication or associated disease, such as a bleeding ulcer a coronary occlusion, portal vein thrombosis, cerebral thrombosis, thrombophlebitis, gout, diabetes mellitus, hypercholesterolemia, or hypertension may initially impress the physician[680 68] In the anicteric patient with polycythemia vera who develops massive unexplained ascites and who is found to have considerable retention of bromsulfalein, the diagnosis of the Budd Chiari syndrome should be entertained[683] (Malignancy is usually considered in these cases) The process can be acute or chronic, and may initially originate either at the ostium of the hepatic veins, in the inferior vena cava, or within the hepatic veins themselves Leukemic degeneration in polycythemia vera does occur, primarily in patients to whom x radiation or P^{3} had been previously administered

With better control of the erythrocytic excess, the high blood viscosity, and the various complications of polycythemia, these patients are living long enough to engender also an undeniably increased incidence of myeloid metaplasia and leukemia[684] It is accordingly very important to exclude the presence of a *relative polycythemia* Relative polycythemia is a chronic condition occurring either without evidence of other disease or appearing in association with chronic vascular or neurologic diseases (A "tension erythremia due to psychologic stress has also been diagnosed by competent hematologists) Only by a study of the absolute erythrocyte volumes or the radioiron clearance from the plasma can a mild case of true polycythemia be distinguished from a normal total erythrocyte mass in the presence of a reduced blood volume

Similarly one must attempt to differentiate primary and relative polycythemia from *secondary polycythemia* caused by congenital heart disease chronic pulmonary congestion, chronic lung disease, pulmonary arteriovenous fistula the Cushing syndrome, and other disorders The presence of oxygen unsaturation along with normal white blood cell and platelet counts in the secondary type help in this differentiation Many reports have already asserted the validity of the concept of secondary polycythemia

megaloblastic arrest of the bone marrow, the clinical picture can closely mimic that of aplastic anemia, leukemia, thrombocytopenic purpura, and subacute bacterial endocarditis [694]

An increased number of patients are being encountered with *combined system disease* but without the typical anemia This may be attributed in part to the presence of folic acid in many multi vitamin preparations which have been taken for the early and unrecognized symptoms of pernicious anemia [695] However, nonanemic patients with combined system disease due to vitamin B_{12} deficiency have been observed in whom folic acid was definitely not taken [696] The estimation of the level of vitamin B_{12} in the serum affords a refined diagnostic method in the evaluation of subacute combined degeneration of the cord when the anemia is mild when other types of macrocytic anemia are considered and after folic acid therapy [697]

Several comments concerning *folic acid therapy and metabolism* are in order It has been occasionally noted that the pregnant patient who de velops a macrocytic anemia will respond to folic acid but not to vitamin B_{12} or to liver extract [698] The reciprocal relation between vitamin B_{12} and folic acid on the metabolic chain that results in the production of nucleic acids has considerable clinical import This has usually related to the hema tologic glo sal and neurologic relapse due to the vitamin B_{12} depletion created by folic acid therapy It has been demonstrated on the other hand, that severe glossitis atrophy of the lingual papillae and cheilosis can develop in patients with addisonian pernicious anemia or nutritional megaloblastic anemia who receive small doses of B_{12} a complication which will respond promptly to folic acid [699] Similarly, Jandl and Lear have clearly shown a deficiency of folic acid to be present in four patients with hepatic cirrhosis and chronic alcoholism exhibiting a macrocytic anemia and a megaloblastic bone marrow [700] These individuals had normal serum vitamin B_{12} levels Small daily doses of folic acid effected striking clinical and hematologic responses

It has been conclusively shown that intestinal anastomoses with resid ual blind loops, gastrocolic fistulae and intestinal strictures in any part of the small or large bowel due to many causes occasionally produce an ab-normal bacterial growth in the small intestine that impairs the utilization of vitamin B_{12} [701] In the absence of one of the tetracycline antibiotics the megaloblastic anemia so induced will not respond to the administration of the intrinsic factor It has also been suggested that on rare occasions pa tients with extensive diverticulosis of the small intestine may develop a blind loop-type of macrocytic anemia as a result of the bacterial stasis and the concomitant production of an abnormal bacterial flora There have been instances of a megaloblastic anemia occurring in association with diverticuli of the small bowel wherein a satisfactory response to the paren teral administration of vitamin B_{12} was forthcoming [701] It is pointed out that neither steatorrhea nor achlorhydria were necessarily present in these cases

Not only must cancer of the stomach be anticipated in pernicious anemia but also the reverse situation—namely the development of this hematologic disorder in patients surviving prolonged periods after a total gastrectomy [70] In fact, MacLean and Sundberg feel that a megaloblastic

platelet levels, and no extramedullary hematopoiesis, it is well to consider the following possible etiologies congenital factors, exposure to toxic chemicals (pp 68 and 385), benign thymoma (p 345),[1063] immune body reactions and hypersplenism, specific metabolic defects (pyridoxine, riboflavin) (p 41), and renal insufficiency [688] A listing and discussion of anemia due to drugs and to radiation is set forth under Group XIII (pp 385 and 401)

The subject of anemia in cancer and the many mechanisms producing this state are discussed in some detail under Group XI (p 324) The careful search for tumor cells in the marrow of a patient with an obscure diagnostic problem can be very rewarding, and has even been suggested as a routine study by Jaimet and Amy in all such cases [689] The presence of immature granulocytes and of nucleated erythrocytes in the peripheral circulation should direct one's attention to either myeloid metaplasia or to a myelophthisic process when a cryptic anemia asserts itself It has been emphasized that the finding of a "dry tap" following repeated attempts at bone marrow aspiration in several sites may be highly significant, not only as being indicative of fibrosis, but also of metastatic neoplasm, lymphoma, and infection [690] Under these circumstances, a bone marrow biopsy should be performed (p 674)

PERNICIOUS ANEMIA AND RELATED DISORDERS

The clinical picture of *pernicious anemia* has actually changed considerably in the past two decades This change is related to the aging of the population, changes in the nature of food, and the earlier seeking of medical care Accordingly, the fever, icterus, profound anemia, splenomegaly, and acute ulcerated glossitis which was so significant in patients with pallor, fatigue and exertional dyspnea in the time of Osler are no longer generally applicable to this era if early diagnosis is to be made

The cutaneous manifestations of pernicious anemia are depicted in Figure 3 (Atlas page 3)

In any analysis of the still commonly overlooked pernicious anemia, other causes of macrocytic anemia as tumors of the right colon, liver disease [700] steatorrhea[153c] (p 40), and the other malabsorption syndromes must be excluded A macrocytic anemia associated with a megaloblastic bone marrow has been observed in a number of patients with panhypopituitarism [109] Pernicious anemia due solely to the dietary deficiency of vitamin B_{12} is extremely unusual, and requires the virtual continuous exclusion of meat fish fowl, dairy products and unrefined grain products for a period of at least two years [691] Brief periods of iron therapy *should not be omitted by therapeutic purists in the early* treatment of severe pernicious anemia once the diagnosis has been made and the reticulocyte crisis demonstrated, since a significant hypochromic anemia can be so induced

It is important to realize that in the presence of infection, an intense myeloid hyperplasia may overcrowd the few megaloblasts present [692] Similarly, the megaloblasts may disappear from the bone marrow *following* transfusion without a rise in the reticulocytes [693] Furthermore, if infection and bleeding complicate the pancytopenia resulting from a nutritional

mononucleosis, disseminated lupus erythematosus and chronic lymphatic leukemia Immunologic studies with certain drugs (Fuadin, Mesantoin phenylhydrazine) suggest that chemical sensitivity—as well as neoplastic diseases and infections—can incite a hemolytic process by altering the antigenicity of the red blood cells and the subsequent production of autoantibodies [706c] Similar immunologic systems may also account for the thrombocytopenia (especially with quinidine) and granulocytopenia induced by an ever increasing list of drugs

Evans and Weiser have recently reviewed their experiences with 41 patients having *autoimmune hemolytic disease* [706b] They stress the false-negative reactions with the direct antiglobulin test (the Coombs test), and the difficulties in demonstrating free serum antibody in these patients with currently available techniques (The presence of free antibody in the serum appears to depend not only upon the amount of this substance being elab orated, but also upon the degree of saturation of the red cell receptors)

It is important to be cognizant of the fact that an individual can have a hemolytic *disease* (that is, diminished survival of the red blood cells) without exhibiting a hemolytic *anemia* if the marrow is capable of com pensating for the excessive destruction The urinary urobilinogen is not as reliable an indicator of active hemolysis as is the fecal urobilinogen since its elevation might represent the inability of the liver to handle the indirect bilirubin rather than the degree of hemoglobin destruction A palpably en larged spleen is not necessary to make the diagnosis of hypersplenism when the cellular elements of the peripheral blood are decreased in the presence of seemingly adequate marrow precursors One of the chief causes for the failure of splenectomy in many patients with autoimmune hemolytic ane mia is that the spleen represents only one of the sources from which autoantibodies can develop

Symptomatic hemolytic anemias have been noted in Hodgkin s dis ease lymphosarcoma chronic lymphocytic leukemia, carcinomatosis, and such nonmalignant entities as systemic lupus erythematosus liver disease and dermoid cysts It has been observed that the anemia in the myelofibrosis myeloid metaplasia syndrome may be related in part to extracor puscular hemolytic mechanisms The occurrence of unexplained weakness cardiac arrhythmias and electrocardiographic abnormalities in the pres ence of a hemolytic process suggests the liberation of large amounts of potassium When confronted with an acute acquired hemolytic anemia it is well to bear in mind that veterans of foreign service are still presenting themselves with delayed and atypical primary attacks of vivax malaria after unusually long periods of incubation [708]

ERYTHROBLASTOSIS FETALIS

The recent review of erythroblastosis fetalis by Allen and Diamond is recommended for its clear and authoritative coverage of this subject and the many important related considerations in the field of immunohema tology [704] Whereas the pathogenesis of this disorder initially appeared to be rather clear cut one decade ago it has at times reached the point of bewildering confusion by virtue of the introduction of many new blood

anemia indistinguishable from pernicious anemia is an inevitable sequel in those patients who survive this *operation for three years or more*[703c] (Accordingly, continuous prophylactic parenteral B_{12} or liver therapy should probably be instituted) The presence of the macrocytic anemia may be obscured by a hypochromic anemia, however, should a gastric cancer (with blood loss) supervene

Even in the presence of other known anemic disorders in patients who have been correctly diagnosed and treated, the possibility of a complicating and unrelated pernicious anemia must not be discounted in this era of increasing geriatric emphasis This is particularly pertinent if an anemia with megaloblastic changes in the marrow persists or recurs, and defies the use of multiple transfusions, steroid therapy, and splenectomy Two such instances were recently reported from one clinic in which pernicious anemia complicated the course of hemolytic disease (idiopathic autoimmune hemolytic anemia in one patient, and well documented, long standing congenital spherocytosis in the other) The typical clinical and hematologic remission was demonstrated following parenteral vitamin B_{12} therapy[703a]

There have been well documented instances of pernicious anemia (i e, inability to absorb vitamin B_{12} and the absence of intrinsic factor activity from the gastric juice) in both children and Negroes[703b] Absent hydrochloric acid is apparently not an indispensable feature of the former since it was found in five or six patients with "childhood" pernicious anemia Perhaps the greatest value of the absorption studies obtained with radioactive vitamin B_{12} is their use to detect pernicious anemia when a remission has been induced by previous therapy (p 683)

THE HEMOLYTIC ANEMIAS AND RELATED DISORDERS

The hemolytic anemias should be kept in mind in cases of cholelithiasis affecting young people and in those patients from various ethnic groups who *are affected in this manner* Deep, chronic, "punched out" ulcers about the ankles in young individuals with anemia should alert one to the possibilities of hereditary hemolytic anemia and sickle cell anemia Although relatively infrequent, ulcers of the leg can also occur in thalassemia (Cooley's anemia) both in males and females, and regardless of the presence or absence of the spleen[720c] Caffey has reviewed a number of the typical and atypical roentgenographic changes in the skeleton in patients with Cooley's anemia[7 0d]

One must diligently search for an underlying systemic etiology if an *acquired hemolytic anemia* is present or suspected, notwithstanding a *negative Coombs test*[706] *While its great value is universally conceded*, the latter procedure is subject to many variables, including the wide range in the potency of commercially available sera bacterial contamination, technical errors the prozone phenomenon and the occurrence of both false-positive and false-negative results (p 680)[707]

Much remains to be learned about the nature of autoantibody production, autoantibody detection, and the role that these immunologic substances play *in vivo* in accelerated blood destruction It is quite probable that a number of diverse mechanisms exist, as in viral pneumonia, infectious

muscular weakness or paralysis—typically involving the lower extremities—with the subsequent passage of dark red urine They are usually precipitated by physical exercise Other muscle groups may be affected by this process of muscle necrosis, including those of deglutition, respiration, and speech Constitutional symptoms (chills, vomiting, melena, and abdominal pain) are often present

It should be noted that a bloody color of the urine, which is benzidine-positive but contains no erythrocytes in the sediment, is as characteristic of myoglobinuria as it is of hemoglobinuria Careful spectroscopic analysis, the absence of discoloration in the blood plasma and muscle biopsy are diagnostic [710] There is also a considerable drop in the total body potassium, along with a profound increase in the serum levels of several enzymes (aldolase, transaminase, phosphohexoisomerase) which are known to be present in high concentrations in skeletal muscle tissue [710b]

A number of instances of '*exercise myohemoglobinuria* have been observed in otherwise healthy young individuals shortly after periods of severe and unusually strenuous exercise, particularly among college students [710d] This disorder is usually characterized by painful and swollen muscle groups the passage of a dark coffee colored urine that tends to clear up within forty eight to seventy two hours and albuminuria with varying numbers of white blood cells The concomitant finding of a low grade fever and hematuria might lead to an erroneous diagnosis of acute glomerulonephritis

SICKLE CELL ANEMIA AND ITS VARIANTS

In sickle cell anemia we encounter another well known "great mimic Physicians who see many Negro patients, particularly in medical or surgical clinics can readily recall cases of this disease that they have variously misdiagnosed as rheumatic fever, osteomyelitis perforated peptic ulcer, acute pancreatitis, renal or biliary calculus and a variety of neurologic or psychiatric disorders [711] [712] While no abnormal hemoglobins were encountered among 910 white persons in one survey which included the Baltimore Galveston and Houston areas, there was an incidence of 11 4 per cent of abnormal hemoglobins among 1405 Negroes as detected by paper electrophoresis (S hemoglobin in 9 4 per cent, and C hemoglobin in 2 2 per cent) [717b] These studies serve to confirm the previous maxim that approximately 10 per cent of the Negro population have circulating sickle cells and that 10 per cent of this group have sickle cell anemia

The incidence of *in situ* pulmonary thrombosis and infarction in the sickle state is so significant that this diagnosis should suggest itself when Negro patients experience episodes of chest pain, unexplained dyspnea or pneumonitis [713b] This is true of both the pure S S disease and the S-variants even when the hematocrit and hemoglobin levels are so high so as to appear to minimize serious consideration being given to an underlying sickle state A vicious cycle can be established by the decrease in the vascular bed of the infarcted lungs, the establishment of an alveolar arterial barrier, severe anemia, recurrent pulmonary infection and acidosis—all subsequently leading to cor pulmonale

types, laboratory procedures, and technical terms (As of July, 1957, there were 49 human blood group "factors" or antigens known to exist, belonging to at least nine genetically independent "systems" or "families") It is pointed out that erythroblastosis of a much less severe type than that stemming from Rh incompatability does infrequently occur on the basis of blood factor A or B incompatability[704b]

In view of the problem of false-negative Rh typing (probably due to the extensive manner in which the blocking antibody covers the red cells of the fetus in certain instances), the Coombs test must be performed to unmask this effect In fact, the diagnosis of erythroblastosis can be almost completely dismissed should the Coombs test on the baby be negative when its blood contains an ABO group that is compatible with the mother, and if no unusual antibodies can be detected in the serum of the mother

Since neither the icterus of erythroblastosis fetalis nor that of physiologic jaundice is usually apparent on the first day, other causes should be considered when this is the case These include infectious hepatitis, bacterial infections (most notably with *Escherichia coli*), hemorrhage, toxoplasmosis, syphilis, torulosis and cytomegalic inclusion disease When the Coombs test is negative in a newborn infant who develops jaundice and no immune antibodies are detected in the maternal serum, one might do well to search for Heinz bodies in the circulating red blood cells Single transfusions have been very beneficial to newborns with a Heinz body anemia when this disorder was not due to poisoning[704c]

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Paroxysmal nocturnal hemoglobinuria may be misdiagnosed as renal disease for years because of the finding of proteinuria casts, and red cells in the urine The red cells may be due to small thromboses in the kidneys, the thrombocytopenia or the glomerular damage caused by the hemoglobin If in doubt the discolored supernatant of a centrifuged specimen readily establishes the diagnosis (p 702)[709] Serious venous thromboses may occur in up to one fourth of patients with PNH The occlusions have occurred in the portal vein, the peripheral veins, and the vessels in the lungs and in the brain When a severe hemolytic anemia and hemoglobinuria affect individuals with an occupational exposure to metals or fumes, the possibility of poisoning due to arsine (hydrogen arsenide) should be entertained (p 69)[253b]

While *syphilitic paroxysmal cold hemoglobinuria* is usually associated with an inactive phase of either late congenital or acquired syphilis, it has been reported during the early active phase of the meningovascular form of this disease[708] It is of interest that the curative effect of intensive penicillin therapy on the infection itself may not become evident on the hemolytic process for some time

IDIOPATHIC PAROXYSMAL MYOGLOBINURIA

The rare condition of idiopathic paroxysmal myoglobinuria (acute recurrent rhabdomyolysis) is characterized by attacks of muscle pain and

head of the humerus with marked flattening and irregularity of the articular cortex) have brought some of these patients to the attention of their physicians[715b]

The absence of sickling and hypochromia in a colored patient with splenomegaly target cells, and mild arthralgia may be due to the related entity of *homozygous hemoglobin C disease*[718] Splenectomy is not indicated in this disease Both hemoglobin S-thalassemia and hemoglobin C-thalassemia can present as either a moderately severe hemolytic anemia or as a microcytic erythrocytosis with little or no reduction in the level of hemoglobin

HEREDITARY LEPTOCYTOSIS

Another source of diagnostic error and unnecessary anxiety stems from the lack of recognition of an asymptomatic case of hereditary leptocytosis (thalassemia minor) This consideration merits reemphasis since the Mediterranean background of many of these patients can no longer be inferred from their last names either because of marriage adoption or change in name The hypochromasia microcytosis lowered hemoglobin content, and the lack of response to the various hematopoietic agents often suggests blood loss or other causes of anemia[719] In addition to the finding of target cells basophilic stippling, normoblastosis, and a decreased osmotic fragility the erythrocyte count almost always exceeds five million per cubic millimeter—a finding infrequently encountered in the presence of blood loss[719b] The elevated or normal serum iron levels in Mediterranean anemia contrast with the low levels in iron deficiency states The bone marrow iron stain has also served as a useful means of differentiating the hypochromic anemia of iron deficiency from the hypochromic anemia of thalassemia[722] Furthermore there is an abnormally high concentration of fetal (F) hemoglobin when electrophoretic and chemical hemoglobin analyses are performed (p 682)

Although the full blown syndrome of *thalassemia major* or *Mediterranean anemia* (severe anemia hepatosplenomegaly leg ulcers bone changes) is primarily a disease of infancy and childhood with a fatal termination it has been encountered in very variable milder forms in patients surviving their fourth and fifth decades[720] Another misconception concerning this disease is pointed out by the fact that well documented instances have occurred in persons of pure Indian Chinese, Negro, German, and English stock[721]

With reference to the more refined studies of iron metabolism, the triad of an increased clearance rate, a relatively high plasma iron concentration, and the poor incorporation of plasma iron into the circulating red cells has been observed only in thalassemia major and in untreated pernicious anemia Although unusual the possibility of hypersplenism as an extracorpuscular mechanism for the anemia should be entertained in atypical instances of this disease in adults ('thalassemia intermedia') that are characterized by the presence of a moderately severe anemia and splenomegaly[720b]

Hepatic cell damage is almost always observed in patients dying of sickle cell anemia, with a high incidence of a macronodular or a postnecrotic type of cirrhosis being encountered [713c] There have been a number of reports which indicate the relative frequency with which gross hematuria can occur in patients with either the sickle cell trait (S-A) or the various abnormal sickle cell combinations, especially that of S-C [713d] There is a high maternal mortality rate and considerable fetal wastage as a result of sickle cell disease [713e] This does not constitute an indication for a therapeutic abortion, however

It is all the more important to maintain a high level of suspicion of this disease inasmuch as its manifestations may occur with a slow blood sedimentation rate (due to the lack of rouleau formation by the sickle cells) and even in the absence of persistent anemia or jaundice [713a, b] Diggs has carefully studied the clinical and hematologic findings in 166 patients with classic sickle cell anemia during 747 clinical crises He has concluded that "the concept of hemolytic crises in sickle cell anemia is a myth" [714]

The cutaneous manifestations of sickle cell anemia are depicted in Figure 89 (Atlas page 57)

It has been shown that patients with homozygous sickle cell anemia (as well as the variant syndromes) can exhibit aseptic necrosis of the femoral head, a condition that may actually be asymptomatic [715a] The finding in Negro children of osseous lesions that are characterized by extreme bone destruction and rapid rebuilding should raise the possibility of bone infarcts due to an underlying sickle cell disease, especially when involvement of multiple bones is noted [715c] The importance of this diagnosis is borne out by the readiness with which these lesions could simulate osteomyelitis, congenital syphilis, metastatic disease, Ewing s sarcoma, tuberculosis and leukemia Since an interval of two to three weeks must usually elapse before the findings become apparent by x ray, many of these bone infarcts are probably not recognized

There appears to be an increased susceptibility to salmonella infection in patients with sickle cell anemia Of further interest is the observation that a salmonella osteomyelitis was present in 31 of 33 cases with this particular combination that have been reported to date in the literature [715d] Multiple foci of bone involvement occurred in two thirds of these patients The potential diagnostic difficulties raised by this issue are apparent when one considers the close radiographic resemblance of osteomyelitis and bone infarction Furthermore fever pain and swelling in the extremities, and leukocytosis can occur either in the presence of osteomyelitis or sickle cell disease alone

Fortunately, the problem of those patients with such atypical features as splenomegaly, target cells, severe hypochromia, and splenic infarction (particularly at high altitudes)[723] has been clarified to some extent by the recent advances in paper hemoglobin electrophoretic studies These studies have shown the existence of several specific types of hemoglobin (A, C D F, and S) which can unite in different genetically determined combinations to produce these clinical variants (p 682) [716, 717] The joint changes are not necessarily limited to the hips in sickle cell hemoglobin C disease since similar painful changes in the shoulders (i e a mottled sclerosis of the

by a false-positive blood serology, it may be attributed to syphilis Most of the eruptions associated with this disease however, actually prove to be caused by drugs or other conditions

A number of observers have felt that infectious mononucleosis is spread primarily by means of mouth to-mouth contact, particularly kissing This concept appears to be supported by the preponderance of this disease in young people and its increased incidence among college students following vacations Another salient epidemiologic point concerns the incubation period which may be as long as five to seven weeks (rather than one or two weeks, as is generally believed)

The diagnosis of 'chronic infectious mononucleosis" should be made *only* after great deliberation, even though this entity probably does exist [730] One of the characteristic features of the hepatitis in infectious mononucleosis is the prompt remission of activity within a period of five weeks, as determined clinically, by functional tests, and in some instances by repeated liver biopsies [331, 731] It is very important to realize that occasional patients with probable infectious mononucleosis may not develop positive heterophile agglutination tests After the prolonged study of a number of these patients and the use of several serologic techniques Leibowitz has arrived at a similar conclusion [732] He attributes this phenomenon either to the existence of several different but related viruses, or to the possibility that such individuals may be serologically "inert" Several new immunologic improvements over the original heterophile agglutination technique that may enhance the serologic accuracy of diagnosis have been developed One of these methods is the ox erythrocyte hemolysin technique in which high titers of hemolysins to ox erythrocytes are often found within the first week of the disease, and persist for six weeks in many instances [732b]

SPLENOMEGALY

There is probably no sign in diagnostic medicine that so consistently evokes the clinician s interest as does splenomegaly whether evidence of a concomitant hypersplenism is present or not [733, 736] Needless to say the first consideration must be whether the particular left upper quadrant mass is in reality an enlarged spleen All experienced clinicians can probably recall instances of various abdominal cysts (pancreatic, mesenteric, ovarian) retroperitoneal neoplasms and tumors of the stomach bowel, or kidney which were initially labeled as instances of splenomegaly

Palpation of the splenic notch, upper gastrointestinal x rays and pyelography may be very helpful in this regard The palpation of a notch" is *not* pathognomonic of an enlarged spleen This finding can also be produced by an irregular tumor of the kidney or by a lobulated cyst of the pancreas There are occasions when it is very difficult to make a differentiation between an enlarged spleen and an enlarged kidney Furthermore, it is possible for a renal tumor to compress the vessels of the splenic pedicle, resulting in a congestive splenomegaly

One of the most embarrassing experiences for any internist is to be informed by either a radiologist or a surgeon that a large spleen is present in a patient whose abdominal examination had been very cursory Super

FAVISM

The occurrence of gastrointestinal complaints and the sudden appearance of a hemolytic anemia in individuals of Mediterranean extraction, followed by hemoglobinuria and jaundice, should not be attributed to a hereditary disorder until favism has been excluded [724] This disorder may result either from the ingestion of the seed of *Vicia faba* or following inhalation of its pollen It usually makes its clinical appearance after a latent period of up to forty eight hours It has a definite seasonal incidence from April to July when the plant blossoms and the fresh, mature beans appear on the market Hepatomegaly and splenomegaly may or may not be present The disease is actually comparatively benign and self limited

INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis can have such protean manifestations that in the absence of a sore throat, posterior cervical lymphadenopathy and fever it may not be suspected until either a blood smear with the characteristic "virocytes" or a positive heterophile antibody determination is found (p 743) [725] Acute infectious mononucleosis has been encountered in patients as old as sixty four years [726] In these older age groups, it is usually mistaken for lymphatic leukemia

Among the complications of this disease are severe mental and neurologic complications (meningoencephalitis, acute polyneuritis), pericarditis, purpura hepatitis and pneumonitis (with or without a pleural effusion) Although unusual both a hemolytic anemia and thrombocytopenia do occasionally occur—in part as the result of an induced hypersplenism—to further confuse the diagnosis [727] The serum transaminase can reflect the presence and the extent of the hepatitis caused by the infectious mononucleosis virus in a very sensitive manner [731b] The direction of the quantitative changes in this enzyme may be of particular value in the nonicteric patient with this disease

Since severe abdominal pain is quite unusual in infectious mononucleosis, its presence should immediately raise the possibility of a splenic rupture particularly if accompanied by a tachycardia and radiation of the pain to the left chest and shoulder [728a] In an analysis of 44 cases of spontaneous rupture of the spleen, Smith and Custer found the incidence of infectious mononucleosis as the underlying cause to be exceeded only by recurrent malaria [728b] The splenomegaly in infectious mononucleosis has been missed either because excessive pressure in palpation caused the examiner to fail to note the soft texture of the spleen, or because palpation was not carried out low enough in the flank

An enanthem consisting of multiple pinpoint lesions on the soft palate, usually near its junction with the hard palate, has been described in over 50 per cent of patients with infectious mononucleosis [729] It appears from the third day to two weeks after the onset of symptoms and may last from three to eleven days (Some clinicians believe that the palatine petechiae are merely nonspecific changes that accompany pharyngeal inflammation) Should a roseola type of eruption occur that is accompanied

Infiltrative Splenomegaly and Tumors

The lipodystrophies (Gaucher s disease xanthomatosis)
The lymphomas
The leukemias
Amyloidosis
Benign tumors and cysts (hemangiomas)

The Collagen Granulomatous Diseases

Systemic lupus erythematosus
Sarcoidosis
Rheumatoid disease
Beryllıosis

The presence or absence of fever, lymphadenopathy, hepatomegaly anemia, bleeding, leukopenia, circulating nucleated red blood cells and evidence of liver failure are particularly important aids in the differential diagnosis of an enlarged spleen It is well to bear in mind that a moderate splenomegaly can occur as a nonspecific response to the chronic hypochromic anemia which results from any type of blood loss On the other hand, splenomegaly does not occur in the presence of a true aplastic anemia Attention was directed in an earlier chapter to the fact that an enlarged spleen might be encountered in the patient with rheumatic heart disease in whom there is no endocarditis (p 115) The presence of purpura in a patient with an undiagnosed splenomegaly is frequently a bad sign, inasmuch as it usually signifies marked marrow involvement due to a generalized leukemic or lymphomatous process If the parasitic diseases are excluded, massive spleens usually signify a chronic granulocytic leukemia myeloid metaplasia lymphosarcoma, and Gaucher's disease

The following associations of various manifestations with splenomegaly have been modified after those set forth by Dameshek and may be of further assistance to the physician confronted by the problematic patient with an enlarged spleen [734b]

Splenomegaly with Fever

Infections including infectious mononucleosis subacute bacterial endocarditis brucellosis
Leukemia or leukosarcoma including Hodgkin s disease
Disseminated lupus erythematosus

Splenomegaly with Pallor and Icterus

Hemolytic anemias of varying types
Cirrhosis of the liver

Splenomegaly with Generalized Lymphadenopathy

Infectious mononucleosis
Chronic lymphocytic leukemia
Lymphosarcomatosis
Hodgkin s disease
R ticulosis
Sarcoidosis

Splenomegaly with Petechiae and Ecchymoses

Acute leukemia
Leukosarcoma with metastases to marrow
Terminal stages of chronic leukemia

ficial as well as deep palpation over the entire left half of the abdomen and flank, the turning of the patient onto the right side, and the use of a firm examining table all contribute to the highest proficiency by the clinician in the recognition of splenomegaly

One should obtain one or several L E cell tests before recommending a "diagnostic splenectomy" or removal of the spleen for "idiopathic thrombocytopenic purpura A number of patients with systemic lupus erythematosus will first manifest their disease after such a procedure[331] Electrophoretic and protein studies of the serum, tuberculin and histoplasmin skin testing, x ray studies of the gastrointestinal tract, the bones, and the chest—in addition to the carefully studied blood smears and bone marrow preparations—constitute other diagnostic procedures that might be employed in undiagnosed splenomegaly

The somewhat controversial techniques of splenic biopsy and splenic aspiration are discussed in Section XI of Part II (p 800)[737] Of these two procedures, splenic puncture with aspiration is far safer It may yield sufficient material with which to make the diagnosis of lymphosarcoma of the spleen, Hodgkin s disease reticulum cell sarcoma and plasmacytoma[736b] The contraindications to this procedure and the importance of not mistaking a nodular mass of white pulp which has been smeared out, for lymphatic leukemia are also indicated in Part II

The following enumeration of the causes of subacute or chronic splenomegaly merits consideration when confronted with this clinical sign

Congestive Splenomegaly

Portal hypertension (cirrhosis of the liver hemochromatosis Banti s syndrome)
Splenic vein thrombosis
Portal vein changes (thrombosis cavernous transformation infection tumor invasion blood dyscrasias)
Extrinsic pressure on the portal or splenic veins
Splenic artery aneurysm (p 299)

Infectious Splenomegaly

Infectious mononucleosis
Subacute bacterial endocarditis
Malaria
Other parasitic diseases (schistosomiasis leischmaniasis echinococcosis)
Hematogenous tuberculosis
Histoplasmosis
Brucellosis
Psittacosis
Lymphogranuloma venereum
Typhoid fever

Hyperplastic Splenomegaly

The hemolytic anemias (hereditary and acquired)
Pernicious anemia
Polycythemia vera
Myelophthisic anemia or myelosclerosis with myeloid metaplasia
Hemoglobin C syndromes
Mediterranean anemia
Thrombocytopenic purpura
Primary splenic neutropenia or panhematopenia
Macroglobulinemia

apparently arise *de novo* or result from several causes, among which are polycythemia vera, metastatic malignancy, benzol poisoning, and myelosclerotic lesions It is characterized by the constant occurrence of extra medullary hematopoiesis in a markedly enlarged spleen and possibly in the liver Considerable myeloid metaplasia has been observed to take place not only in these organs but also in the kidneys, the adrenals, the pituitary and the pancreas [739] Unless considerable hemorrhage supervenes, however it is most unusual for the cellular infiltration associated with such extra medullary hematopoiesis to result in adrenal failure or decreased liver and kidney function This compensatory mechanism for damage which is limited to the bone marrow contrasts with the absence of any such response in an aplastic anemia, wherein the entire reticuloendothelial system has been injured or destroyed

There is usually an associated anemia with nucleated red cells and immature white cells in the circulating blood marked weakness, a bleeding or bruising diathesis and at times a leukemoid total white cell count The simultaneous occurrence of immature cells in *both* the red cell and the white cell series is emphasized as being of the greatest value in distinguishing this condition from leukemia Bone marrow studies and biopsies from the lymph nodes liver or spleen obviously will aid in establishing the diag nosis The presence of an increasingly severe hypochromic anemia and bone marrow hypoplasia are usually indicative of spent polycythemia" as the cause of myeloid metaplasia When a hyperuricemia is found its level is more apt to be proportional to the peripheral white cell count than is the case with the elevated serum uric acid levels in chronic myelogenous leukemia or polycythemia vera

The concomitant occurrence of hemorrhagic and thrombotic compli cations is prominent in this myeloproliferative disease and focuses attention upon the qualitative changes in the platelets This situation is in contrast to the relatively normal platelet function in chronic myelogenous leukemia and in polycythemia vera [739] In fact there is often a preponderance of megakaryocytes not only in the hypoplastic bone marrow, but in many organs of the body Defective platelet formation in the presence of abundant megakaryocytes may represent inhibition by splenic or humoral mechanisms

In the presence of a concomitant severe thrombocytopenia or a hemolytic anemia, splenectomy may not be contraindicated, as was previously taught [741] There are several complications of splenectomy when performed for a myeloproliferative syndrome that must be kept in mind however These include the increased susceptibility to infection (particularly if corti sone or its related steroids are also administered) and the occurrence of profound intravascular thrombosis [739]

Splenomegaly with Plethoric Appearance

Polycythemia vera

Splenomegaly with Bone Changes

Severe thalassemia
Gaucher s disease
Myelofibrosis with myeloid metaplasia
Multiple myeloma
Amyloidosis
Metastatic carcinoma

Splenomegaly as an Isolated Phenomenon

Nonspecific hyperplasia
Primary splenic neoplasms
Gaucher s disease
Sarcoidosis

Splenomegaly with Cytopenias (particularly leukopenia and thrombocytopenia)

Infections characterized by a reticuloendothelial response (typhoid paratyphoid malaria syphilis tuberculosis kala azar histoplasmosis)
Granulomas (particularly sarcoidosis)
Portal hypertension
Nonspecific hyperplasia
Neoplasms of the spleen (primary lymphosarcoma reticulum cell sarcoma endothelioma hemangioma cyst)
Miscellaneous (disseminated lupus erythematosus rheumatoid arthritis or the Felty syndrome)

Splenomegaly with Elevated White Counts

Infections
- Pyogenic infections particularly those involving the spleen (subacute bacterial endocarditis splenic abscess brucellosis and others)
- Infectious mononucleosis
- Certain cases of measles poliomyelitis psittacosis and other infections

Leukemia and disseminated leukosarcoma
- Granulocytic lymphocytic monocytic leukemia—acute and chronic
- Disseminated lymphosarcomatosis
- Reticulosis

Myeloproliferative disorders
- Polycythemia vera
- Myeloid metaplasia
- Thrombocythemia

Hemolytic anemia
- Most types

MYELOID METAPLASIA (MYELOPROLIFERATIVE DISEASE)

Myeloid metaplasia has consistently proved to be a perplexing diagnostic problem Physicians who do not bear this condition in mind may be readily led astray by its superficial resemblance to leukemia and Banti s syndrome One should be particularly suspicious of this entity when patients with polycythemia vera are diagnosed as developing chronic myelogenous leukemia particularly when the diagnosis is based solely on an analysis of their peripheral blood counts [738] Also in a chronic anemia in which there is considerable variation in the size and shape of the red cells, but without hypochromia and without an adenopathy—either in the presence or absence of hemolysis and hyperplasia of the bone marrow—myeloid metaplasia is likely [740]

Myeloid metaplasia is a clinical and pathologic syndrome that can

It should be noted that certain organs which are commonly affected in sarcoidosis are rarely involved by tuberculosis and the other granulomatous diseases These sites include the skin the bones of the hands and feet, the lacrimal and parotid glands (very characteristic), and the heart On the other hand, it is most unusual for this disease to produce draining sinuses or to affect the pleura pericardium, peritoneum and adrenal glands—areas which are often invaded by the tubercle bacillus Likewise it is distinctly unusual for sarcoidosis to extend through the wall of the bronchus and to involve the bronchial mucosa Such cases do occur however and present themselves as hemoptysis, high fever pneumonitis, and atelectasis [745] The importance of entertaining the possibility of sarcoidosis in the presence of every unexplained mediastinal enlargement—even when it is unilateral and not associated with demonstrable involvement of other organs—will be further considered under the discussion of mediastinal tumors (p 339)

The cutaneous manifestations of sarcoidosis are depicted in Figure 27 (Atlas page 18)

With reference to the skeletal involvement it has been shown by complete bone surveys that involvement of the other bones is infrequent even when lesions are present in the hands and feet Although the latter are usually asymptomatic and not diagnostic by themselves they occur frequently enough in sarcoidosis to be of considerable value [746a] The hypercalcemia and hypercalciuria in sarcoidosis suggest endogenous vitamin D intoxication These effects have been successfully treated with both cortisone and sodium phytate agents that apparently increase the fecal excretion of calcium [746b] (Since the relationship of tuberculosis to the causation of sarcoidosis is still debated it may be wise to concomitantly administer isoniazid in patients with sarcoidosis who are to be treated with the steroid hormones)

Other diagnostic considerations which were heretofore academic are no longer so regarded with the availability of recent therapies This is evidenced for example by the rapid spread of pulmonary tuberculosis or blastomycosis after a patient—misdiagnosed as having sarcoidosis—is intensively treated with the adrenocortical steroids Furthermore a number of systemic mycotic infections have been reported in patients with Boeck s sarcoid including cryptococcosis blastomycosis coccidioidomycosis, and histoplasmosis [747]

In addition to the hyperproteinemia the hypercalcemia and the elevated gamma globulin one may obtain considerable help from the tuberculin test, the liver biopsy and a biopsy of either the peripheral or scalene lymph nodes (p 798) in making this diagnosis The cutaneous unresponsiveness of patients with sarcoidosis often represents a nonspecific suppression of previous tuberculin sensitivity It is due to both local and systemic immunologic factors since it can also be demonstrated when other cutaneous antigens of the delayed tuberculin type reaction are introduced Random skeletal muscle biopsies have not been sufficiently utilized in attempting to establish the diagnosis of sarcoidosis (p 796) [748]

The pathologic features unfortunately are not always pathognomonic Neither has the Kveim test been completely reliable inasmuch as it is

GROUP VII

Noninfectious Granulomata

SARCOIDOSIS

BERYLLIOSIS

WEGENER'S GRANULOMATOSIS

THE HISTIOCYTIC RETICULOENDOTHELIOSES
The Hand Schuller Christian Syndrome
Eosinophilic Granuloma
Letterer-Siwe Disease
Lipogranulomatosis

SARCOIDOSIS

SARCOIDOSIS is a chronic process of undetermined cause It may exhibit a clinical picture ranging from the benign asymptomatic case, incidentally discovered on a routine chest film to the most perplexing diagnostic problem involving multiple systems of the body in a seriously ill patient The numerous controversies and misconceptions of this disease attest to its frequency and importance These concern the relationship of sarcoidosis to tuberculosis its supposed greater incidence in certain racial groups and geographic areas the cutaneous anergy and the proper classification of some of its manifestations in isolated organs—to mention but a few of these unraveled facets

The following brief listing of the organs that may be involved in this disorder and some of their unusual clinical variations serves to remind the reader of the scope of this problem [742, 785]

Skin and mucous membrane lesions
Lymphadenopathy
Splenomegaly (hypersplenism)
Hepatomegaly
Parotid gland (uveoparotid fever)
Lungs (miliary, reticulated fibrotic nodular and mixed types fibrinoid necrosis and cavitation pneumothorax alveolar-capillary block)
Bones (punched-out or reticulated lesions with intact periosteum polyarthritis)
Heart (heart block cor pulmonale congestive failure)
Central nervous system (facial palsy seizures)
Genitourinary system (nephrocalcinosis uremia epididymitis)
Endocrine glands (anterior pituitary hypofunction syndrome diabetes insipidus)

and the lower respiratory tract, (2) a generalized focal necrotizing vasculitis involving both arteries and veins especially in the lungs, and (3) a glomerulitis of a focal, necrotizing, thrombotic, and widespread nature

Clinically, therefore, this "disseminated pathergic granulomatosis" can present itself as a nonresponding case of sinusitis chronic pneumonitis (particularly of the so-called cholesterol type),[451] extensive cartilagenous and bony destruction (producing the saddle-nose" deformity), orbital involvement progressive renal damage, hemoptysis and hemorrhages from the skin and mucous membranes In addition there may be transient episodes of arthritis, neuritis carditis, eosinophilia, parotitis, prostatitis, and unexplained fever [757 759]

THE HISTIOCYTIC RETICULOENDOTHELIOSES

The histiocytic reticuloendothelioses are a group of nonfamilial, generalized granulomatous disorders frequently characterized by the secondary deposition of lipid (usually cholesterol) Since they may merge from one into another, it is not unlikely that these conditions will subsequently be found to be variants of a single entity, possibly of an infectious nature Notwithstanding this possibility that they might represent different phases of the same disorder—especially from the pathologist s point of view—the wide divergence of their course and prognoses justifies their clinical separation (It should be pointed out that certain pathologists disagree with the unitarian etiologic and pathogenetic concept of the Hand Schuller Christian disease the Letterer Siwe disease and eosinophilic granuloma of bone They regard such an orientation as an oversimplified classification of widely diversified clinical disorders often based on the study of an atypical transitional ' case)[763b]

The bony changes in all are similar These consist of destruction of the trabeculae, a central area of rarefaction and occasionally the erosion or actual widening of the cortical portions of the bone Periosteal proliferation is infrequently observed however

THE HAND-SCHULLER CHRISTIAN SYNDROME AND EOSINOPHILIC GRANULOMA

In adults the course may be chronic and protracted (as in the Hand Schuller Christian syndrome) or it can be very benign (as in eo inophilic granuloma) Bone lesions visceral involvement skin rashes petechiae, honeycomb lungs eye and posterior pituitary involvement have all been noted in the former disorder [760 765] The skull (and more particularly the calvarium) is the most common site of bone involvement, with soft tissue nodules often being palpable in the scalp overlying the defects in the bone The lesions are characterized by the presence of eosinophiles foam cells, and accumulations of histiocytes A chronic diffuse pulmonary fibrosis with impaired alveolar capillary diffusion is found in some cases of the Hand Schuller Christian syndrome [765c]

The diabetes insipidus is usually insidious in its onset and presumably stems from involvement of the pituitary stalk or the hypothalamus Asso-

frequently positive in patients with tuberculosis and negative in some patients with sarcoidosis (p 796) [749] In view of our present state of confusion concerning the sarcoid process, it is wise to use the term "pseudosarcoid" and an appropriate prefix (as beryllium pseudosarcoid or helminth pseudosarcoid) for cases which are not classic One instance in particular is *lipogranulomatous pseudosarcoid* These lipogranulomas are associated with asteroid bodies in giant cells, and can be focal or diffuse They may be due to the absorption of oil from the intestine, fat necrosis, or disturbed lipid metabolism [750]

BERYLLIOSIS

Notwithstanding the recent advances in the prevention of beryllium poisoning and its declining incidence, this diagnosis must be kept in mind because of the long latent periods involved (up to ten years) [751 753] This is more significant in the case of chronic pulmonary granulomatosis than the chronic subcutaneous granuloma due to the implantation of the beryllium phosphor Beryllium disease follows inhalation of beryllium metal, some alloys of this element with other metals, certain beryllium oxides, and the acid salts of beryllium (especially the sulfate and fluoride), but not of the beryl ore itself Instances of beryllium poisoning have been reported from almost every state in the union, and have resulted from a wide variety of operations (fluorescent lamp manufacturing or salvage, beryllium extraction or metallurgy ceramics, radio tube manufacturing, atomic energy development) This diagnosis is also important from a medicolegal standpoint since the pulmonary form may occur as a nonoccupational disease ("neighborhood beryllium poisoning) in people living within a quarter mile radius of beryllium plants [755]

Long before the exertional dyspnea, cyanosis clubbing, and cor pulmonale are evident, the patient may complain merely of weight loss, weakness, and easy fatigability It is not unusual to find the roentgenologic changes preceding the clinical symptoms by as much as two years [754] The disturbance in calcium metabolism in beryllium poisoning has led to a number of instances of renal calculi Neither the cystic bone changes nor the ocular, tonsillar or parotid lesions that are so characteristic of sarcoidosis have been observed in this disease [756] Furthermore, there are no reported cases in which hilar lymph node enlargement was present without concomitant densities in the lung field When doubt exists, biopsy of the lung and submission of the specimen to definitive spectrographic analysis might be recommended (p 795) It has been the general experience that this "cirrhosis of the lung is much more favorably affected by steroid therapy than is pulmonary sarcoidosis

WEGENER S GRANULOMATOSIS

Wegener's granulomatosis is an entity that has been described clinically only in recent years It is probably related to but distinct from, periarteritis nodosa It is characterized by the threefold pathologic process of (1) necrotizing granulomatous lesions in the upper nasal air passages

cutaneous lesions may resemble intertrigo or seborrheic dermatitis (p 789)[767d]

The exception to all rules of diagnostics is again evidenced by the authentic reports of several cases of the Letterer Siwe disease occurring in adults[767] It is of interest that several of these instances of adult Letterer Siwe disease have manifested themselves in the form of a severe macrocytic anemia with steatorrhea This was a result of the widespread mesenteric lymph node involvement—at times present several years before the occurrence of a palpable lymphadenopathy or hepatosplenomegaly[767c]

LIPOGRANULOMATOSIS

The newly described syndrome of lipogranulomatosis is mentioned because of the rather unusual clinical manifestations of this lipoglycoprotein storage" disease and its resemblance to both the lipoidoses and the Hand Schuller Christian and Letterer Siwe disorders A familial component may be present In a careful study of three of these patients by Farber and his colleagues a rather similar clinical pattern of sensitivity and swelling of the extremities accompanied by a hoarse weak cry emerged shortly after birth[768]

Although the similarity to rheumatoid arthritis was impressive, this diagnosis could be excluded by the onset of the disorder in the immediate neonatal period along with the distinctive histologic picture The finding of foam cells might tend to implicate Niemann-Pick's disease but the hepatosplenomegaly that is so characteristic of this disorder was not observed in lipogranulomatosis While a foam cell granuloma complex is also found in the Hand Schuller Christian and Letterer Siwe disorders they predominantly involve the bones liver spleen and lymph nodes Furthermore, the lipoglycopeptides encountered in lipogranulomatosis are quite different chemically

ciated destruction of the sella turcica is infrequent in this disease paradoxically, there may be no evidence of the endocrinopathy when it is found In one series of 29 patients, *refractory chronic otitis media* (unilateral or bilateral) was the most frequent presenting complaint This was associated with overt changes by x ray in the mastoid or petrous portions of the temporal bone in three fourths of these individuals[761] The exophthalmos may likewise be either unilateral or bilateral, and is usually accompanied by destruction of the orbit Ulcerative lesions of the gums, and single or multicystic areas of destruction in the tooth bearing portions of the mandible might also serve as diagnostic clues

The cutaneous eruption in the Hand Schuller Christian syndrome often first appears in the neck, the antecubital spaces, and the axillae as brownish red, papular, and sometimes scaly lesions The small nodules or firm infiltrated patches may resemble sarcoid Deep, sharply delineated, and ulcerated granulomatous lesions involving the skin of the inguinal, perianal, perineal, and vulvar regions—as well as the buccal mucous membrane—that show the microscopic picture of eosinophilic granuloma often have other skeletal and endocrine counterparts of "histiocytosis X" uncovered by further study[762]

The cutaneous manifestations of the Hand Schüller Christian syndrome are depicted in Figure 13 (Atlas page 9)

The finding of a *single eosinophilic granuloma* in one bone must accordingly initiate not only a complete skeletal survey, but also careful study of the skin, lungs, liver, lymph nodes, and bone marrow for evidence of visceral involvement It should be remembered that the blood cholesterol and lipid levels are normal in these conditions ("essential xanthomatosis *of the normocholesterolemic type*") *Similarly*, a peripheral blood eosinophilia is not usually encountered even though tissue eosinophilia at the site of the local lesion is prominent[761]

Letterer Siwe Disease

The prevailing consensus is that acute nonlipid disseminated reticuloendotheliosis (Letterer Siwe disease) is the infantile form of a disease spectrum which in other age groups encompasses the Hand Schuller *Christian syndrome and eosinophilic granuloma*[766] *The disease is usually fatal and is characterized by hepatosplenomegaly, a rapidly progressive* anemia, skin eruptions adenopathy, destructive bone lesions, and a variety of secondary infections (pharyngitis, gastroenteritis, impetigo, thrush, pneumonitis and meningitis) Unlike disseminated histoplasmosis, which may produce a strikingly similar clinical picture, no organisms can be *cultured*

The cutaneous manifestations of the Letterer Siwe Disease are depicted in Figure 14 (Atlas page 10)

The unit lesions consist of focal aggregations of large pleomorphic mononuclear cells These have been readily demonstrated in the corium of the skin, the bone marrow, and the liver The use of the touch preparation technique, in which the induced cutaneous exudate is studied, has aided in the diagnosis of Letterer Siwe disease, especially inasmuch as the early

EMBOLISM

IN THE PRESENCE of multiple acute manifestations or complications affecting the patient with heart disease (mitral stenosis, myocardial infarction endocarditis, and endomyocardial fibroelastosis), obesity, inanition, varicosities, and in the postoperative and postpartum states, multiple embolism must always head the list of possible causes by virtue of potentially life-saving prophylactic and therapeutic considerations This is equally applicable to the venous and the arterial networks of the circulation [769, 771] Cerebral vascular accidents and pulmonary renal intestinal arterial, and retinal embolism—with or without actual infarction—are cited to remind the physician of the clinical extent of this problem Phlebothrombosis, thromboembolism and cerebral thrombosis must be regarded as occasional sequelae of rapid diuresis with its induced hemoconcentration and increased blood viscosity [77, 773] Even though a bacterial endocarditis may have been sterilized by the administration of the antibiotics the vegetative material that remains on the surfaces of the valves might give rise to embolic phenomena [4, b, 784b]

A number of isolated reports have called attention to the fairly characteristic clinical picture of *embolic occlusion of a patent foramen ovale* [781] This diagnosis should be suspected when a patient without apparent heart disea e develops peripheral thrombophlebitis which in turn is followed by pulmonary and systemic embolism with persistent cyanosis Electrocardiographic evidence of acute cor pulmonale may or may not be found since the interatrial shunt can permit decompression of the hypertension induced in the right side of the heart Sudden death with bulging neck veins and intensification of the cyanosis is another striking feature of this syndrome

It is not generally appreciated that episodes of *arterial thrombosis and embolism* can also occur as manifestations of malignant disease [78] An unexplained apoplexy has at times been the first clue to an underlying malig nancy In these instances the apoplexy has been frequently due to aseptic embolism rather than to tumor emboli or cerebral metastases Embolism from either a bacterial invasion of the heart valves or from marantic and aseptic thrombotic endocardial vegetations in patients with carcinomatosis or other debilitating diseases was discussed previously (p 117) [416, 417] It has been suggested that the arteriolar and capillary changes, the phlebitic lesions, and the degenerative verrucal endocardiosis in patients with car cinoma might represent an immunoallergic response[783] —perhaps to the altered proteins elaborated by the neoplasm—rather than being due to a secondary generalized intravascular coagulation process [783b]

In the absence of a septal papillary muscle or valvular rupture, sud den death occurring in patients with endocarditis should suggest *coronary artery embolism* The myocardial infarction secondary to coronary embol ism from an underlying bacterial endocarditis may primarily involve the right ventricle [784b] Similarly sudden death in young patients with throm bophlebitis of the lower limbs or the pelvis should raise the possibility of paradoxical coronary embolism via a patent foramen ovale [784]

If there is good reason to suspect an acute *embolus to the superior mes enteric artery* an urgent embolectomy should be undertaken if irreversible

GROUP VIII

Vascular Diseases

EMBOLISM

Venous Arterial Occlusion of a patent foramen ovale Coronary artery Superior mesenteric artery and its small branches Cholesterol crystal embolism Atheromatous emboli following surgery on the aorta Pulmonary embolism

THROMBOSIS AND THROMBOPHLEBITIS

Pulmonary veins Mesenteric vessels Renal veins Gangrene of the extremities of venous origin

THROMBOANGIITIS OBLITERANS

PREMATURE CALCIFICATION WITHIN THE MEDIUM SIZED VESSELS

FAT EMBOLISM

DECOMPRESSION SICKNESS

THROMBOHEMOLYTIC THROMBOCYTOPENIC PURPURA

IDIOPATHIC VISCERAL THROMBOPHLEBITIS MIGRANS

RAYNAUD'S DISEASE RAYNAUD'S PHENOMENON, AND "SYMMETRICAL DIGITAL GANGRENE"

CRYOGLOBULINEMIA

REFLEX SYMPATHETIC DYSTROPHY

THE CERVICODORSAL OUTLET SYNDROMES

THE CARPAL TUNNEL SYNDROME

TEMPORAL ARTERITIS

HEREDITARY HEMORRHAGIC TELANGIECTASIA
Asymptomatic Microhematuria

THE ALLERGIC NONTHROMBOCYTOPENIC PURPURAS (HENOCH SCHONLEIN)

PSEUDOHEMOPHILIA

"ALLERGIC" VASCULITIS

THE DERMATOLOGIC PURPURAS (MAJOCCHI, SCHAMBERG, GOUGEROT BLUM, HUTCHINSON)

ANGIOKERATOMA CORPORIS DIFFUSUM UNIVERSALE (FABRY)

glucose and saline solutions) in patients who develop pulmonary embolism [776b]

In place of the characteristic pleurisy, dyspnea, and hemoptysis, pulmonary embolism may present itself as fever, dyspnea, vague pleuritic chest pains, syncopal or anxiety attacks, angina pectoris, congestive failure paroxysmal auricular fibrillation, vague epigastric distress, "primary" pulmonary hypertension[777d, 870] hyponatremia, and the triad of tachycardia, digitalis toxicity and mercurial fast edema [776, 778] An attack of gallbladder colic may be simulated by an infarct at the base of the right lung [160]

One must constantly bear in mind that pulmonary embolism need not necessarily result in typical pulmonary changes (p 129) [454] The manifestations of thrombophlebitis in the lower extremities have occasionally first appeared several days following a pulmonary embolus A right ventricular gallop rhythm may be heard over the lower sternal area in patients with acute pulmonary embolism [866d]

The finding of a transient inversion of the T waves over the right precordium in this disorder is highly important it should not be mistaken for an anteroseptal myocardial infarction Similarly while it is not specific for pulmonary embolism the demonstration of elevated ST segments in the electrocardiographic "window leads" (i e leads in which the R wave is absent—usually due to a previous myocardial infarction—and which therefore might register the intracavitary potentials induced by subendocardial ischemia) may serve as a valuable clue to its presence [776b] The determination of the serum transaminase while not always characteristic, has already proved to be of great value in differentiating pulmonary embolism from acute myocardial infarction (p 694)

Insufficient attention has been paid to the pelvis as a source of recurrent pulmonary emboli This is particularly true in women where there is a freely anastomosing and valveless pampiniform plexus formed by tributaries of the ovarian fallopian, and uterine veins (which in turn, usually drain into the renal vein on the right and into the inferior vena cava on the left) This complication is very prone to take place in pelvic varicoceles, whether primary in nature or secondary to such disorders as pelvic inflammatory disease retroversion of the uterus, venous obstruction by masses or tumors and the venous stasis associated with cardiac disease [775b] When this source is being considered the finding of radiographically opaque phleboliths may assume some significance

In male patients with multiple pulmonary emboli in whom the veins of the lower extremities are apparently free of disease considerable attention should be given to the possibility of emboli originating from thromboses in the prostatic plexus [775a]

THROMBOSIS AND THROMBOPHLEBITIS

Thrombi tend to occur infrequently *in situ* in the pulmonary veins for various reasons (the constant motion of the lungs the protection against trauma offered by the chest wall, and the level of the pulmonary veins being close to that of the heart) *Pulmonary venous thrombosis* may develop

necrosis of the bowel is to be prevented Instances of such surgical success are few, but nonetheless on record [789c] The presence or absence of pulsations in the superior mesenteric artery at the time of operation is much more significant than the color of the bowel The clinician is apt to be misled by the temporary alleviation of the initial symptoms (severe pain in the back and abdomen, vomiting, collapse) and the little abdominal tenderness and spasm that precedes the development of frank necrosis of the bowel

On rare occasions, small emboli are able to lodge in the vessels of the bowel wall, producing ischemic necrosis with ulceration or partial obstruction rather than a massive infarction of the bowel In the several instances where this phenomenon has been reported, the terminal ileum and the cecum were the principal areas affected [789b]

On occasion *cholesterol crystal emboli* arise from eroded atheromatous plaques, particularly in the abdominal aorta and superimposed upon a syphilitic mesaortitis The ensuing granulomatous endarteritis with its ischemic atrophic complications is most apparent in the encephalomalacia and renal vascular changes (with or without hypertension) that have been described [783]

The importance of considering the possibility of *atheromatous emboli to the kidneys after* the performance of *surgery on the aorta* for either aneurysmal or occlusive disease will be discussed in a later chapter (p 444) [911e]

Pulmonary Embolism

Pulmonary embolism has probably become the most common disease of the lungs encountered in general hospitals In their extensive study of 90 patients with this disorder Israel and Goldstein found the following dominating clinical patterns [776b]

1 Predominant respiratory manifestations in 39 (pneumonitis dry pleurisy pleural effusion and simulating either a lung abscess tuberculosis or cancer of the lung both clinically and by x ray)

2 Predominant cardiovascular manifestations in 33 (congestive failure cor pulmonale and simulating either a myocardial infarction coronary insufficiency or the post infarction syndrome)

3 Predominant abdominal manifestations in 6 (simulating an acute condition within the abdomen a subdiaphragmatic abscess or primary hepatic disease)

4 Predominant central nervous system manifestations in 4 (syncope convulsions and hemiplegia)

Establishing the diagnosis of a pulmonary embolus, fatal or otherwise that has resulted from a previous accident or injury may have a significant bearing upon insurance benefits The tendency for "silent' thromboses to occur in the deep leg veins of tall men—most notably after prolonged sitting, effort, or strain—should also be borne in mind when previously healthy individuals are suddenly affected with obscure edema or chest pain [774] One must not overlook the causative role of the iatrogenic traumatic phlebitis produced by repeated venipunctures the prolonged insertion of polythene tubes in the veins, and the intravenous infusion of many irritating diagnostic and therapeutic substances (bromsulfalein, hypertonic

gression of a venous thrombosis or embolism when it is due to an underlying malignancy poses a valuable clue that is not generally appreciated [787b]

Three other factors which should be sought out in patients who develop thrombophlebitis or arterial occlusion without obvious organic cause include (1) the wearing of girdles and other clothing that bind in the fold of the groin, especially during prolonged periods of travel, (2) unusual strain or sitting over protracted periods by tall men, and (3) television viewing while sitting with the legs immobile and in an awkward position for long periods [774]

Subcutaneous thrombophlebitis involving the veins of the breast and chest wall is a benign and self limited condition that should not be mistaken for a lymphangitic carcinomatous spread or a symptomatic thrombophlebitis [789] Furthermore one must be careful not to confuse thrombophlebitis with the traumatic neuritis and myositis of the legs that is produced by various mechanical means, most particularly the pressure exerted by the patella on the important vascular and nervous structures from the habit of repeated crossing of the legs

Gangrene of Venous Origin in the Extremities

Internists and surgeons alike are not generally cognizant of the fact that gangrene of the extremities can be of venous origin even though this is very infrequent [780] By virtue of the abundant venous pathways and the relative ease with which a collateral circulation is established, tissue anoxemia usually does not evidence itself following thrombophlebitis or phlebothrombosis However should the majority of the tributaries also be occluded—in addition to involvement of the main venous channel—marked anoxemia of the tissues and possibly gangrene can eventuate The entire arterial system of the extremity must be shown to be patent either by palpation arteriography or by actual dissection before this diagnosis can be made Angiospasm appears to play a secondary role Gangrene of venous origin has been described as a sequence of thrombosis involving the entire venous system from the iliac to the dorsalis pedis veins in patients with malignancy [780b]

The most frequent train of events leading to the gangrene is as follows a sudden onset phlegmasia alba dolens or "milk leg" (the initial feature in one half of the cases reported), early cyanosis which develops rapidly and extends to the entire extremity, excessive edema of a wooden consistency and the demonstration of patent peripheral arteries In 9 of 27 cases reviewed by Haimovici the arterial pulses were palpable [780a] The skin temperature may be conserved, which contrasts with the other signs of vascular deficit Active bleeding from the proximal end of the main artery during amputation is an added diagnostic feature in favor of this diagnosis The readiness with which this condition might be confused with arterial embolism is at once apparent

Inasmuch as the gangrene tends to remain superficial and limited a conservative surgical attitude is justified In fact, a major amputation could possibly be averted if the diagnosis is correctly made Furthermore,

however, on the basis of a long standing pneumonitis, carcinoma, sickle cell disease (p 195), pulmonary infarction, bronchiectasis, and other disorders of the lungs or blood vessels It might also possibly give rise to systemic emboli [779] It has been shown that careful dissection of the smaller pulmonary veins in such instances will reveal the source of these emboli [779b]

Considerable fluid formation may appear both within the intestine and the abdomen following a *thrombosis of the superior mesenteric vein* Another radiographic clue to the presence of mesenteric infarction is the scarcity of gas shadows in the bowel [136c] The mesenteric venous thrombosis that follows nonpenetrating traumatic injuries to the abdomen may produce an ileus either shortly after the injury or several weeks later [1381b]

While thrombosis of the superior mesenteric vessels is forty times more frequent and usually results in an acute condition within the abdomen, *thrombosis of the inferior mesenteric vessels* is apt to present a less acute and a more confusing picture because of the greater possibilities of partially establishing a collateral circulation The finding of a sharply demarcated rigid and narrow segment in the splenic flexure of the colon with a pseudopolypoid appearance by barium enema may be the clue to an inferior mesenteric vascular occlusion [789]

Acute mesenteric infarction has also been observed in some cases of *the Leriche syndrome* This complication is due to an acute ascending thrombosis taking place above the level of the aortic obstruction and involving the major mesenteric arteries The Leriche syndrome will be discussed further in the following chapter (p 299)

The presenting clinical picture of a *renal vein thrombosis* is influenced by the rapidity and completeness of occlusion of the vein When acute, there is a severe, constant, and persistent pain in the loin that may radiate to the groin or testicle Fullness, tenderness, and muscle spasm in the loin, enlargement of the kidney seen by x ray, transient hematuria proteinuria (often followed by the nephrotic syndrome), and at times thromboembolism in the lungs, limbs, and pelvis then ensue [187] When the occlusion is very gradual the nephrotic syndrome may be the sole manifestation (p 55) Anticoagulant therapy and surgery have been observed to reverse a previously relentless downhill course [187b]

Thrombophlebitis

When spontaneous thrombophlebitis occurs or recurs a second time and cannot be readily explained, a systemic etiology predisposing to thrombus formation must be sought out, particularly among the neoplasms, the collagen diseases, and polycythemia vera [785, 786] (Certain families also exhibit a profound thrombotic diathesis) The same applies to pulmonary embolism of a cryptic nature Neither the presence of long standing varicosities, chronic venous insufficiency, a marked periphlebitic reaction nor the concomitant occurrence of Raynaud's phenomenon necessarily eliminates this possibility [787] This complication may occur not only in pancreatic carcinoma, but also in malignancy involving the ovary, stomach lung breast, or prostate The failure of anticoagulant therapy to prevent pro-

Cerebral fat embolism can result in confusion, convulsions, rigidity, coma, or a mild psychosis Oval fat masses in the retinal vessels and subhyaloid hemorrhages have been seen Petechial hemorrhages make their appearance over the upper chest, shoulders, and even in the mucous membranes on or about the third day Fat may also be detected in the sputum and urine after this time (p 709)

These considerations are valuable since the patient will usually recover completely if he can be kept alive for one week after the onset of cerebral symptoms Furthermore certain orthopedists who have been interested in this problem have found that it is possible to cause sequestration of the released fat in an extremity during an extensive operation upon bone by employing a tourniquet This apparently prevents the fat droplets from reaching the systemic circulation [794b] When the possibility of fat embolism is raised, Love and Stryker have suggested the use of intravenous 5 per cent glucose–5 per cent alcohol infusions for the emulsifying action of this combination, and of heparin for its activating effect on the lipoprotein lipase [794a]

The renal failure in acute pancreatitis has been attributed in part to fat embolism resulting from the fat necrosis [795a] The glomerular capillaries are first blocked with the peritubular circulation being subsequently affected Similarly, in 7 of 67 necropsied cases due to fatal acute hemorrhagic pancreatitis evidence of fat necrosis was found, presumably due to the dissemination of large amounts of lipase via the peritoneal and transdiaphragmatic lymphatics [795b] The diagnostic importance of this observation as it relates to fat embolism is probably very limited however

DECOMPRESSION SICKNESS

The physician who is likely to deal with divers or fliers both in and out of the military must harbor considerable respect for the diagnostic elusiveness of decompression sickness particularly in this age of jet aircraft and atomic submarines Behnke has observed that "the nascent gas bubble is replacing the spirochete as the great imitator [796a] The manifestations of this disorder result from the formation or growth of bubbles of gas (and not initially to hypoxia) on exposure of the body to a too rapid and large decrease in the barometric pressure primarily due to the liberation of nitrogen from solution They are essentially the same whether the individual is decompressed from sea level pressures to altitudes of 25 000 feet or above or from high pressure to sea level pressure as in the case of caisson disease In either instance the preventative measures (denitrogenation) and therapy (recompression) are similar

This condition should be differentiated from the fatal air embolism that is encountered as a result of submarine escape training In this situation, the air enters the pulmonary circulation through alveolar capillaries that have been ruptured by the overdistention of the lungs from excessive intrapulmonary air pressure [796b] The problem of air embolism following surgery, childbirth and diagnostic procedures is considered under Group XV (p 444)

The clinical features of decompression sickness can be more readily

one must bear in mind that in "blue thrombophlebitis," the cyanosis and ischemia are often transient

THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans will occasionally also involve the mesenteric, coronary, cerebral, and renal vessels [790] It can even secondarily damage the heart valves Edwards has suggested a possible relationship to the rheumatic diseases when it occurs in women [791a] The clinician is cautioned against making this diagnosis too often, since even the busiest practitioners of peripheral vascular disease encounter true Buerger's disease *very infrequently* nowadays It is further emphasized that the pathologic changes are quite peripheral, and that most cases of intermittent claudication which are being so diagnosed ultimately prove to be instances of primary arteriosclerotic vascular disease Progressive arterial disease is not necessarily the consequence of a phlebitis migrans, even when the latter represents a manifestation of Buerger's disease [791b]

The cutaneous manifestations of thromboangiitis obliterans are depicted in Figure 42 (Atlas page 26)

PREMATURE VASCULAR CALCIFICATION

Although no significance is attributed in most instances to the presence of premature calcification within the medium sized vessels, one would do well not to overlook a concomitant diabetes mellitus, Cushing's syndrome, Paget's disease of bone, or the various causes of hypercalcemia when the sclerosis is very marked in the presence of unexplained illness Several reports have described instances of parathyroid adenomas or carcinomas in which extensive calcinosis was a major presenting feature, as manifested by striking calcification of the vessels, along with signs and symptoms of arterial insufficiency and even gangrene of the extremities (p 25) [69, 77] When further doubt exists, the examination of a biopsy specimen from a small artery or from the area of the phlebitis may be most helpful

FAT EMBOLISM

Pulmonary and cerebral fat embolism resulting from injury to bone (especially simple fractures of the tibia or femur), extensive soft tissue injuries, and less commonly from operations in which large amounts of fat are excised or unduly traumatized is a potentially important diagnosis that still remains infrequently considered [792] Although it was difficult to delineate clear cut clinicopathologic pulmonary or cardiac syndromes, fat droplets were found by Scully in approximately 90 per cent of 110 patients who had died at military hospitals up to four weeks following battle trauma [793]

A symptom free interval, ranging from several hours to ten days, usually precedes the onset of symptoms in fat embolism Pulmonary manifestations may vary from tachypnea with fever to severe pulmonary edema

warding It is pointed out that "*platelet thrombosis with thrombocytopenia* usually occurs as a complicating syndrome with other diseases rather than as a separate disease entity [800] These include the leukemias, the rickettsial infections, the dyscollagenoses, malignancy and aplastic anemia

Even though splenectomy has appeared to induce a remission in classic thrombohemolytic thrombocytopenic purpura cognizance should be taken preoperatively of the possibility that this disorder might be a manifestation of lupus erythematosus In such an instance the L E cell phenomenon and other evidences of the latter entity could first become apparent in the post-splenectomy state [798o]

IDIOPATHIC VISCERAL THROMBOPHLEBITIS MIGRANS

It is of interest that in both thrombohemolytic thrombocytopenic purpura and in idiopathic visceral thrombophlebitis migrans, the lungs are infrequently primarily affected In the latter entity the fever leukocytosis, eosinophilia, massive pleural effusions, the nephrotic syndrome, and infarction of the intestines, spleen and adrenals can produce such confusing clinical pictures that they are ultimately diagnosable only by microscopic examination [801] The same applies to the thrombosis of the superior or inferior vena cava, the hepatic veins, and the portal vein which may result from this process

RAYNAUD S PHENOMENON RAYNAUD S DISEASE AND SYMMETRICAL DIGITAL GANGRENE'

The symptom of *Raynaud s phenomenon* is cited as a reminder of the numerous serious organic and functional diseases that may be initially manifested by its appearance Edwards has presented a comprehensive differential diagnosis of this condition [802] It will suffice for the present to merely recount such possible underlying causes as neurovascular compression the 'thoracic outlet syndrome the collagen disorders polycythemia, leukemia cold agglutination cryoglobulinemia and radiation injury along with the aforementioned Buerger's disease and thrombohemolytic thrombocytopenic purpura In addition to the obvious association of secondary Raynaud s phenomenon with its underlying disease the following criteria have been set forth as aids in differentiating it from primary Raynaud s disease

1 Exposure to a cold environment or to an emotional stress does not necessarily precipitate the phenomenon when it is a symptomatic feature

2 Secondary Raynaud s phenomena are frequently neither bilateral nor symmetrical

3 In the secondary form particularly when due to thromboangiitis obliterans or to arteriosclerosis obliterans, gangrene is apt to be much more extensive [803a]

The occurrence of simultaneous phasic changes in several digits is frequently evidence of a more serious and progressive form of the under lying disease In the added presence of bizarre dependent redness and hemorrhage the clinician would do well to think of polyarteritis and sys-

comprehended when it is recalled that these gas bubbles occlude numerous vessels (chiefly the veins and capillaries), collect in tissues (most notably fat), and create pain by distorting nerve endings in this manner When tension is exerted on the fascial planes about the joints, "bends" are experienced A very high protein diet appears to predispose to bends [796c] The term "chokes" refers to the inability to inspire without inducing a cough or sense of constriction in the throat or chest It is due to the accumulation of bubbles in the pulmonary vessels and possibly also to an acute cor pulmonale Violent gas pains in the abdomen result from the expansion of gas in the gastrointestinal tract, and can be obviated to some degree by a high fat diet Adiposity apparently predisposes to aeroembolism, presumably by virtue of the fact that the fat is an important reservoir for nitrogen, and that during decompression to altitude more nitrogen is liberated in the obese [796d] The focal cerebral signs and irreversible shock occurring in five airmen who were exposed to simulated altitudes of 30,000 to 38,000 feet in decompression chambers were caused by demyelinization, perivascular gliosis, and fat embolism

Another pursuit that is already resulting in decompression sickness and air embolism is the increasingly popular sport of "skin diving" among the general populace, both with and without underwater breathing apparatus [796e] In view of the lack of knowledge about the hazards involved—in contrast to the training of military divers using SCUBA (self contained underwater breathing apparatus)—civilian physicians in the coastal and lake areas should become familiar with them The urgency for an accurate diagnosis is underscored by the fact that permanent neurologic sequelae or death can take place if immediate treatment by recompression and subsequent proper stage compression is delayed This consideration and the potential diagnostic difficulties that might be encountered were set forth by Johnson in the case of a civilian skin diver who surfaced too rapidly and without periodic stops after spending prolonged periods at a depth of 90 feet He experienced a paraplegia that could be differentiated from an infectious myelitis or a Guillain-Barré syndrome only after great deliberation and a ten hour delay in the institution of recompression [796f]

THROMBOHEMOLYTIC THROMBOCYTOPENIC PURPURA

The most interesting entity of thrombohemolytic thrombocytopenic purpura has recently been reviewed by several authors, most notably by Adelson [797, 798] He concludes that an autoimmune process against the red blood cells, platelets megakaryocytes, and vessel walls is probably present The pathognomonic lesion consists of a homogeneous eosinophilic material which partially or completely occludes the arterioles, capillaries, and rarely the venules, but interestingly, there is a striking lack of infarction and inflammatory reaction [799] Fever, multiple and diffuse neurologic signs and symptoms, purpura, petechiae of the skin and mucous membranes, bleeding from the body orifices, extensive gangrene of the skin and subcutaneous tissues, and other constitutional symptoms occur

The diagnosis may be made by blood studies skin biopsy, and aspirated marrow embedded in paraffin Muscle biopsies are usually not re-

highly characteristic of cryoglobulinemia Unfortunately, the diagnosis of this phenomenon in the laboratory is at times not at all clear cut since such substances as cryofibrinogens, heparin precipitable cryofibrinogens, and cold agglutinins may be responsible for it (p 686) There is no regularly demonstrable relationship between the amount of cryoglobulins and the presence or severity of the Raynaud phenomenon or cold purpura

Although it is most frequently found in multiple myeloma, this disorder has also been encountered in leukemia, adenocarcinoma kala azar rheumatic fever, hepatic disease, subacute bacterial endocarditis polycythemia vera, Raynaud s disease and disseminated lupus erythematosus It is of significance that only rarely is the Bence-Jones protein detected in the urine or is a false-positive Wassermann reaction noted in essential cryoglobulinemia, in contrast to their frequent occurrence in myeloma

The plasmacytosis and cryoglobulinemia that are associated with certain malignant tumors may be evanescent often disappearing after removal of the tumor This sequence of events has been interpreted as a phase in the immune response to cancer [807] It is the result of observations such as these that have indicated to many pathologists and clinicians a probable basic interrelationship between plasmacytosis hyperglobulinemia, cryoglobulinemia, amyloidosis, the dyscollagenoses myeloma, and hypersensitivity states

REFLEX SYMPATHETIC DYSTROPHY

Reflex sympathetic dystrophy with its excessive and prolonged pain vasomotor disturbances, delayed functional recovery and trophic changes may result from many disorders at different anatomic sites in the neck, shoulder girdle, or upper extremity It should be recognized and treated as soon as possible after a myocardial infarction or a hemiplegia in order to avoid incapacitating or irreversible sequelae The author has been impressed by the frequency with which this localized condition is variously diagnosed for long periods of time as arthritis syringomyelia, cerebrovascular disease gout, scleroderma and a host of other disorders This is also the experience of many others [808]

THE CERVICODORSAL OUTLET SYNDROMES

Pain, weakness, loss of sensation, and a variety of neurovascular signs and symptoms in the neck shoulder chest wall and upper extremities are commonly seen as a result of the compression or stretching of the neurovascular structures in the region of the cervicodorsal outlet The inclusive designation of the cervicodorsal outlet neurovascular syndrome includes a number of specific and nonspecific mechanisms for such compression or stretching These consist of the cervical rib syndrome the scalenus anticus syndrome the subcoracoid pectoralis minor syndrome (also referred to as the hyperabduction syndrome) the costoclavicular syndrome, the first thoracic rib syndrome poor posture anxiety tension states and brachialgia statica paraesthetica (stiffness and paresthesias in the hands occurring during sleep)

temic lupus erythematosus The Raynaud phenomenon, with or without arterial occlusive changes, accompanied thrombophlebitis in 4 of 15 cases reported from the Mayo Clinic in which the latter sign alerted the clinician to the diagnosis of unsuspected malignant disease [787a] There have appeared reports of significant numbers of patients, however, with "*symmetrical digital gangrene*" *due to multiple arterial occlusions*, with or without pyrexia, in whom no primary arterial or cardiac disease, infection, thrombophlebitis, blood dyscrasia, poisoning or other cause could be found [804]

Gangrene of the fingers in polyarteritis is depicted in Figure 40 (Atlas page 25)

Time and experience have proved the validity of the criteria employed by Allen and Brown in making the diagnosis of *Raynaud's disease* As noted above, these consist of the following (1) the induction of attacks of the Raynaud phenomenon by emotion or cold, (2) the bilaterality of the Raynaud phenomenon, (3) the absence of gangrene (or if it is present, its very limited and minimal nature), (4) the absence of other primary disorders that could account for the Raynaud phenomenon, including occlusive arterial disease, central nervous system disease, and cervical ribs, and (5) the persistence of symptoms for at least two years

A *nonocclusive symmetric peripheral gangrene* has been observed after prolonged vascular collapse in a variety of conditions These include cardiac shock due to a number of disorders (acute myocardial infarction, congestive failure, mitral ball valve thrombus tight mitral stenosis, prolonged tachycardias), pulmonary infarction carbon monoxide poisoning, and many severe infections (pneumonia, meningococcemia, cholera, tuberculosis) [871k] [1] In these individuals, not only are the femoral and pedal pulses readily palpable, but the larger blood vessels to the affected area are patent by actual dissection The institution of intensive vasopressor therapy appears to bear little relationship to this particular complication

CRYOGLOBULINEMIA

A few additional comments are in order concerning the previously mentioned entity of cryoglobulinemia This term was first coined by Lerner and Watson in 1947 when they described a patient whose serum contained a cold precipitable protein, and whose presenting symptom was an excessive purpura that developed on exposure to cold [805] In addition to these manifestations and the Raynaud phenomenon, other patients have demonstrated mottling and ulceration of the extremities, bleeding from the nose and gums extensive retinal hemorrhages, melena, arthritis, renal involvement, progressive deafness, cold urticaria, anemia, agglutination of red blood cells with rouleau formation, and a rapid sedimentation rate [806] [807] The precipitation of the abnormal cryoglobulin concomitantly enmeshes the red cells and causes the formation of a viscid gel with sludging This probably obstructs the flow of blood through the smaller vessels, both in the periphery and in the pulmonary and renal arterial networks It also incites a subsequent local reaction with secondary thrombosis, ischemia, and necrosis

Cold precipitation of the serum which is reversible on warming is

trointestinal, respiratory, or genitourinary tracts, their presence is a most significant clinical observation particularly if the possibility of a pulmonary arteriovenous fistula also exists.[812-813] Vascular hemangiomata (angioma, phlebectasia, and hamartoma) and telangiectasia form integral parts of several unusual syndromes (the Maffucci syndrome, adenoma sebaceum, and the germ plasm dysplasias) which are further described under Group XIV.

The cutaneous manifestations of hereditary hemorrhagic telangiectasia are depicted in Figure 41 (Atlas page 25).

Much of the attention has been directed in hereditary telangiectasia to the large arteriovenous fistulas of the lung as an explanation for the classic triad of cyanosis, clubbing of the fingers, and polycythemia. Nevertheless, one must not lose sight of the fact that small multiple arteriovenous aneurysms of the same order as those on the skin can also occur, without there being any large lesions of the saccular type.[81d,e] These small lesions *cannot* be detected by arteriography. They may be inferred, however, from the results of cardiac catheterization and pulmonary function studies—information which may prove of considerable value if the diagnosis of a congenital heart malformation is being entertained.

ASYMPTOMATIC MICROHEMATURIA

The management of asymptomatic microhematuria is a problem quite commonly encountered by urologists and merits comment at this point. Prostatic hyperplasia, urethritis, and a host of other benign processes account for the erythrocyturia in more than 90 per cent of these cases, particularly in patients under the age of fifty years.[814] *"Athletic pseudonephritis"* is an entity that may be readily confused with acute glomerulonephritis in the case of the athlete engaged in strenuous activity (especially football) who concomitantly happens to develop a sore throat.[815] The hematuria (gross or microscopic), proteinuria, and cylindruria—which might otherwise be considered as pathognomonic of parenchymal renal disease—usually clear within one week. The entity of "exercise myohemoglobinuria"—in which severe and strenuous exercise in otherwise healthy young individuals is followed by painful, swollen muscle groups, albuminuria, and dark colored urine—is discussed elsewhere (p. 195). This disorder has also been mistaken *for acute glomerulonephritis*.[719d]

In addition to the number of angiomatous and vascular lesions resulting in hematuria that have already been elaborated upon, the syndrome of hereditary hematuria, nephropathy, and deafness is germane to this subject. It will be further amplified under Group XIV (p. 423). Attention was called in a preceding chapter to the frequency with which individuals who harbor either the S-A or S-C sickle cell traits can present themselves with gross hematuria (p. 196).[713d]

The author has encountered the problem of a presumed microhematuria which actually turned out to be an instance where prostatic spherules were being mistaken for red blood cells. Their smaller size, the absence of biconcavity and crenation, their persistence after the addition of acetic

These entities are notorious for being overlooked by those who are not aware of their clinical ramifications They are often labeled as rheumatoid arthritis, Raynaud's disease, Buerger's disease, the shoulder hand syndrome, periarthritis, peripheral neuritis, various neurologic disorders (protrusion of a cervical intervertebral disk, syringomyelia, progressive *muscular dystrophy), and a superior sulcus tumor* [809] *The thoracic outlet* syndrome may cause serious trauma and pathologic changes in both the subclavian artery and the carotid artery, possibly even resulting in "pulseless disease" (p 301) While the various outlet maneuvers (the Adson test, the Allen test, hyperabduction of the arm, forced depression and retraction of the shoulder girdle) are of considerable value in many instances, definitive emphasis should not be attributed to them, either for diagnosis or for decisions concerning surgery

THE CARPAL TUNNEL SYNDROME

The presence of numbness, shooting pains, burning sensations, swelling and contractures affecting the palmar surfaces of the first three digits and of the radial aspect of the fourth digit on one or both hands constitutes the so called carpal tunnel syndrome This median nerve neuritis may occur in such systemic diseases as myeloma, amyloidosis, acromegaly, and rheumatoid arthritis [208] Its inclusion in this section is prompted by the fact that it is usually misdiagnosed as the shoulder hand syndrome, Raynaud's disease, or multiple sclerosis

TEMPORAL ARTERITIS

Temporal *arteritis is cited to remind the clinician that* systemic manifestations and a significant mortality at times accompany the exquisitely painful, tender, and thickened superficial temporal arteries in this condition These features include malaise muscular and joint pains, weight loss, anorexia, a low grade fever, anemia, *leukocytosis, and an elevated* sedimentation rate [810] Pathologically there is a necrotizing, proliferative, and granulomatous panarteritis that may affect not only the temporal vessels, but also the visceral and retinal arteries (Up to one third of these patients develop visual impairment or blindness) While the disorder usually tends to be self limited, the diagnostic resectional biopsy of the involved vessel may be curative in the more severe cases (p 801) [811] The adrenal steroids appear to be definitely indicated in certain patients with temporal arteritis, primarily as an effective means of safeguarding the remaining vision [sub]

The cutaneous manifestations of temporal arteritis are depicted in Figure 44 (Atlas page 27)

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Any discussion relating to the subject of the commonly unrecognized vascular diseases must include hereditary hemorrhagic telangiectasia It is surprising how often the characteristic lesions on the face, tongue and lips can be found *if* they are looked for In undiagnosed bleeding from the gas

and thromboplastin generation)[815c] This disorder also appears to be more closely related to vascular pseudohemophilia than true hemophilia A (AHF deficiency) or hemophilia B (PTC deficiency) in that females are commonly affected and because of the great differences in its genetic propagation from that of sex linked hemophilia

ALLERGIC VASCULITIS

"Allergic vasculitis of varying degrees of severity also appears to be the common denominator in a number of conditions of uncertain etiology, but in which the hypersensitivity factor is strongly implicated, both clinically and pathologically The antibiotics, numerous drugs various infectious agents, and malignant tumors may serve as the underlying antigenic stimuli in evoking this nonspecific response, particularly when trauma, thrombosis, and embolization are ab ent A number of clinicians and pathol ogists have attempted to define the entity of "hypersensitivity angiitis' as distinct from periarteritis both etiologically and pathologically[943 949 95]

Peripheral edema, fever, weight loss subcutaneous nodules pneumonitis, dermatitis muscle tenderness and weakness, urticaria, neuritis, and renal failure have been described, in addition to the aforementioned purpura gastrointestinal bleeding and arthralgia In one comprehensive and well documented series of 30 living patients with this type of vasculitis—in whom neither the presence of systemic lupus erythematosus nor periarteritis was demonstrable—18 could be classified as having one of the fol lowing five clinical syndromes contact dermatitis with generalized sen sitization or an ' id reaction, urticaria with angioneurotic edema vascular purpura erythema nodosum and dermatomyositis[819] Except when complicated by renal failure removal of the antigen and institution of one of the adrenocortical hormones will usually promote healing and sclerosis

An acute generalized vasculitis may complicate the course of malignancies especially when metastatic involvement has taken place[956c] This possibility should be entertained when a patient harboring such a neoplasm suddenly exhibits a rapidly progressive and fatal uremia since there is apt to be an extensive necrotic glomerulitis

THE DERMATOLOGIC PURPURAS

There is a group of disorders known as the dermatologic purpuras which usually affects the lower extremities and produces punctate pig mented macules The lesions are at first reddish they then change to the brownish color of hemosiderin and finally fade almost completely The group is composed of purpura annularis telangiectodes (Majocchi) progressive pigmentary disease (Schamberg) pigmented purpuric lichenoid dermatosis (Gougerot and Blum), and angioma serpiginosum (Hutchinson) In 92 cases studied at the Mayo Clinic no constant clear cut histologic differences could be found to warrant further separation[8 0] The fundamental defect is increased capillary fragility which is usually not associ ated with demonstrable hematologic abnormalities Although these disorders rarely affect the general health of the patient, they are usually not

acid, and their abundance in the prostatic secretions can aid in this differentiation

THE ALLERGIC NONTHROMBOCYTOPENIC PURPURAS

Those who have been perplexed by the periodic syndromes of the allergic nonthrombocytopenic purpuras (Henoch Schonlein) can attest to the variegated manifestations of vascular allergy [816, 817] The various features include coalescing purpuric lesions over the limbs, joint symptoms, acute abdominal pain with melena, and an acute glomerulonephritis These may occur together or they may appear as isolated symptoms

The cutaneous manifestations of the Henoch Schonlein syndrome are depicted in Figure 6 (Atlas page 5)

Except for the tourniquet test, the usual blood studies (platelet counts, bleeding time, clotting time, prothrombin time) are normal The fundamental lesion is apparently an antigen antibody type of vasculitis and perivasculitis which not infrequently follows an antecedent infection of the pharynx or tonsils

Handel and Schwartz have called attention to the striking small bowel changes produced by areas of transitory edema in patients with the Henoch Schonlein syndrome [816c] The diagnostic difficulties in establishing the coexistence of Henoch's purpura and an actual intussusception will be discussed later, along with the gravity of this situation if it remains unrecognized (p 496) [816b]

The problem of purpura will be further considered under Group XVII (p 519)

PSEUDOHEMOPHILIA

No attempt will be made to elaborate upon the ever increasing number of derangements in the blood clotting mechanism (See pp 677–681 in Part II and the corresponding references) Brief mention should be made, however of the entity described under the titles of vascular hemophilia, pseudohemophilia the von Willebrand syndrome, "constitutional capillaropathies, and hereditary hemorrhagic diathesis [818] These individuals have a tendency to bleed easily as a result of the transmission of this diathesis by autosomal genes either as mendelian dominants or recessives

The defect may consist only of a vascular derangement In this case the markedly prolonged bleeding times (preferably performed by the Jacobson technique) (p 677) are accompanied by normal clotting times, normal platelet counts, normal clot retraction and normal prothrombin consumption [818b] This situation contrasts with that of hemophilia in which the bleeding time is normal The hemorrhage may occur from any of the mucous membranes, intracranially into the joints vaginally and after dental extractions It may be controlled by the use of normal plasma and cortisone [818d]

Pseudohemophilia type B is a similar entity It differs from the uncomplicated vascular pseudohemophilia by virtue of an associated antihemophilic globulin deficiency (as manifested by poor prothrombin consumption

GROUP IX

Diseases of the Heart and Great Vessels

OBSCURE HEART FAILURE AND CARDIAC ENLARGEMENT—Differential Diagnosis

"High output failure" Orthostatic hypernatremia Hyperthyroidism Auricular fibrillation Fatty infiltration of the heart Polycythemia of obesity Rheumatic carditis Endomyocardial fibroelastosis Myocardial fibrosis Myocarditis Chagas heart disease Acute glomerulonephritis Cor pulmonale Bernheim s syndrome Tricuspid stenosis Atrophy of the heart Senescence of the myocardium Arteriovenous fistula of the heart Estrogen therapy Impaired sensitivity of the respiratory center resulting in alveolar hypoventilation Idiopathic myocardial failure occurring in the last trimester of pregnancy and in the puerperium Myocardial sarcoidosis Primary systemic amyloidosis Primary cardiac amyloidosis Cirrhosis of the liver Glycogenosis of the heart Gargoylism

ATYPICAL MANIFESTATIONS OF HEART FAILURE

Asthma Hemoptysis Localized interlobar pleural effusions Left vocal cord paralysis Distention of azygos vein Hepatogenic hypoglycemia Insomnia during nocturnal recumbency Nocturnal angina Nonproductive cough Pleural effusions Unrecognized edema

IMPORTANT CLUES IN CARDIAC PHYSICAL DIAGNOSIS

POTENTIAL IATROGENIC HAZARDS IN THE MANAGEMENT OF HEART FAILURE

Cerebral manifestations Gastrointestinal manifestations Rhythm disturbances and digitalis intoxication Electrolyte and fluid imbalances The sequelae of bed rest Other therapeutic hazards

PERICARDITIS

Symptomatic Fat necrosis involving the parietal pericardial fat Pericardial tamponade Constrictive pericarditis

LESIONS SIMULATING MITRAL STENOSIS

Myxoma of the left atrium Constricting mediastinitis

promptly recognized as benign purpuras outside of dermatologic circles, and accordingly tend to incur much diagnostic anxiety and expense

ANGIOKERATOMA CORPORIS DIFFUSUM UNIVERSALE

An infrequent systemic condition that may be readily confused with the various purpuras, hereditary telangiectasia, and certain skin disorders is described by the rather cumbersome title of angiokeratoma corporis diffusum universale (Fabry) The term "angiokeratoma" refers to the small, raised and partially hyperkeratotic vascular aneurysms that are present on the skin The lesions are at first restricted to the lower part of the trunk or the upper part of the lower extremities, with a centripetal distribution in groups

The cutaneous manifestations of angiokeratoma corporis diffusum universale are depicted in Figure 43 (Atlas page 26)

Various organs are also affected by these aneurysms, including the retina, joints, myocardium, lungs, and gastrointestinal tract Hypertension, vasomotor disturbances, and uremia have been found to be associated with this condition An interesting renal syndrome may occur, consisting of proteinuria, isosthenuria, hematuria, cylindruria, and the presence of free and intracellular birefringent bodies in the urinary sediment [81]

THE CAROTID SINUS SYNDROME

Chemodectomas (carotid body tumors)

SYNDROMES PRODUCED BY DISSECTING ANEURYSMS OF THE AORTA

Chronic (healed) dissecting aneurysms

SYNDROMES PRODUCED BY NONDISSECTING ANEURYSMS OF THE AORTA

Thoracic aneurysms (luetic, arteriosclerotic, traumatic) Aortic sinus aneurysms Aneurysms of the coronary arteries Abdominal aneurysms Splenic artery aneurysms Mycotic aneurysms

ANOMALIES AND DISORDERS OF THE GREAT ARTERIAL TRUNKS

"Selective arterial occlusion "Abdominal angina"

The Leriche Syndrome
Buckling of the Aortic Arch
Buckling of the Descending Aorta
Buckling of the Common Carotid Artery
Buckling of the Innominate Artery
Persistence of the Left Superior Vena Cava
Chronic Obliteration of the Great Arterial Trunks

OBSCURE HEART FAILURE AND CARDIAC ENLARGEMENT

THE CLINICIAN must always be alert to a possible systemic cause of obscure heart failure or cardiac enlargement when the usual stigmata of coronary, hypertensive rheumatic, congenital, and syphilitic heart disease are absent[3, 145] It should be noted that every experienced clinician has encountered the occasional patient with symptoms due to an enlarged heart in whom a definitive diagnosis was impossible, either because the patient recovered or because of the paucity of specific findings at postmortem examination[822] The following entities may present themselves as unusual instances of cardiomegaly or congestive failure

Metabolic disorders

Primary amyloidosis (pp 59 and 235)[202]
Hemochromatosis (p 60)[212]
Xanthomatosis (p 77)[277, 278]
Beri beri (p 43)[833]
Wernicke s syndrome (p 43)[142e]
Glycogen storage disease (p 76)[829c]
Adiposity of the heart (p 232)[145]
Post-starvation refeeding (p 234)[841b]
Poisonings (carbon tetrachloride emetine)[87, 238]
Hypoproteinemia[131]
Orthostatic hypernatremia (p 231)[810]
Cirrhosis of the liver (pp 98 and 235)[829]

Collagen and hypersensitivity diseases

Lupus erythematosus (p 305)[92, 831]
Polyarteritis (p 307)[843]

Constrictive pericarditis Constrictive endocardial sclerosis Thoracic deformities Congenital deformities of the heart *Verrucous and healed endocarditis Relative mitral stenosis* Thyrotoxicosis Ball valve thrombus of the left auricle

AORTIC VALVULAR DISEASE

The diverse clinical manifestations of aortic stenosis and aortic insufficiency

SOME IMPORTANT ASPECTS OF MULTIVALVULAR DISEASE

Aortic stenosis and mitral stenosis Aortic insufficiency and mitral stenosis Mitral regurgitation and aortic insufficiency Tricuspid stenosis and mitral stenosis

DIFFERENTIAL DIAGNOSIS OF MYOCARDIAL ISCHEMIA

Symptomatic Nonatheromatous causes of myocardial ischemia

COMPLICATIONS AND SEQUELAE OF MYOCARDIAL INFARCTION

Perforation of the interventricular septum Rupture of a papillary muscle Rupture of the left ventricle Infarction of either atrium, with or without rupture Aneurysm of the left ventricle Pericardial involvement Pleural involvement Pulmonary involvement *Mediastinal emphysema* Abscess formation in the heart Obstruction by an intramural thrombus Symmetric peripheral gangrene Embolization and hemiplegia Hiccups Reflex sympathetic dystrophy and the postcoronary anterior chest wall syndrome Complications of therapy

PULMONARY HYPERTENSION AND PULMONARY HEART DISEASE

"Ayerza's disease" Thrombosis of the major pulmonary arteries Stenosis of a main branch of the pulmonary artery Enlargement of the pulmonary conus pulmonary artery segment area Pectus excavatum Therapeutic hazards attendant upon the presence of pulmonocardiac failure

GENERAL CONSIDERATIONS PERTAINING TO THE DIAGNOSIS OF CONGENITAL HEART DISEASE

COMPLICATIONS AND VARIATIONS OF PATENT DUCTUS ARTERIOSUS AND THE TETRALOGY OF FALLOT

ORTHOSTATIC HYPOTENSION AND OTHER POSTURAL CARDIOVASCULAR PHENOMENA—Differential Diagnosis

Chronic postural hypotension The syndrome of left lateral hypotension Postural shock in the latter part of pregnancy Postexertional orthostatic hypotension Orthostatic hypernatremia The effects of posture on the electrocardiogram and rhythm formation

SYSTEMIC HYPERTENSION—Differential Diagnosis

Parenchymal renal disease Renal vascular disease Diffuse vascular disease The endocrinopathies *Other causes*

nary embolism, cor pulmonale, and metastatic malignancy. The concept of "isolated left ventricular failure" may be very misleading. It is well to bear in mind that the slower the heart rate, the more normal the appearance of the QRS in the electrocardiogram, or the thinner the patient, the more severe the damage to the myocardium must be in order to precipitate clinical heart failure.

1. The presence of a "*high output failure*" may be one of the first clinical manifestations of thyrotoxicosis, beri beri, systemic arteriovenous fistula, anemia, and Paget's disease of the bone.[83f] Inasmuch as Paget's disease of the bone is an affliction that chiefly affects the older age groups, a number of clinicians have questioned the frequency with which heart failure actually arises on this basis alone.[829f] Contributing to the cardiovascular derangements in severe Paget's disease of the bone is the high incidence of marked calcification involving both the aortic and mitral valves.

The incidence of high output circulatory failure resulting from the formation of an arteriovenous fistula during the course of a nephrectomy or intervertebral disk surgery is probably greater than that indicated by the 11 cases reported to date in the English literature. This complication is the aftermath of inadvertent injury to the close lying great vessels (especially the iliacs) during such a procedure. This injury has been readily overlooked by both the experienced surgeon and anesthetist.[844c] The patient may then present with evidence of heart failure years later.

2. When dealing with the problem of the patient with "refractory heart failure," it is well to be sure that he is lying in the recumbent position to the best of his respiratory tolerance. This stems from the observation that there is a greater excretion of sodium, chloride, and water in this position than in the sitting posture, presumably related to the vasoconstriction and diminished renal perfusion with *orthostatic hypernatremia* that is induced by the upright position.[310] Furthermore, it has been repeatedly shown that mercurial diuresis can be potentiated by recumbency (p. 251).[310b]

Clinicians should be suspicious of high sodium intake even by the cooperative intelligent patient if a refractory state of heart failure exists. Certain foods stated to be low in salt actually contain much more sodium than is desirable. A spot check of the amount of urinary chlorides by one of several simple tests (p. 701) can be helpful.

3. Even the most experienced of cardiologists are time and again fooled by the cardiovascular manifestations of *hyperthyroidism*. It is again emphasized that this diagnosis must be given careful consideration when confronted with unexplained auricular fibrillation (paroxysmal or persistent), a tachycardia persisting under the influence of sleep or sedation, atypical angina pectoris, obscure cardiomegaly, and the presence of heart failure that does not respond to conventional therapy.[40] One must not lose sight of the fact that the failure of the heart in hyperthyroidism might also be aggravated by the relative thiamine deficiency that is found in this state.

4. A number of reports have clearly pointed out the fact that *auricular fibrillation* can occur in the absence of hyperthyroidism in hearts that are basically normal—even to the point of producing heart failure.[834]

5. The author has called attention to the infrequently considered

Scleroderma (p 309)[440, 442, 444]
Fiedler s myocarditis[8, 817]
Hypersensitivity reaction[824]

Hematopoietic disorders

Pernicious anemia (p 190)
Sickle cell anemia and its variants (p 195)[711, 712]

Infections

Bacterial endocarditis (p 114)[401]
Diphtheria (p 161)[482, 484]
Trichinosis (p 173)[821, 823]
Viral myocarditis (p 233)[8, 816]
Chagas disease (p 233)[831]

Endocrinopathies

Thyrotoxicosis (p 231)[401]
Cushing s syndrome (p 28)[27, 29]
Myxedema (p 16)[24, 26]
Acromegaly (p 30)
Estrogen therapy (p 234)[1183]

Vascular

Arteriovenous fistula (peripheral pulmonary cardiac) (pp 223 and 234)[812]
Pulmonary embolism (p 212)[777, 778]

Myocardial and Pericardial Neoplasms (p 325)[1033, 1034]

Primary
Metastatic
Lymphomatous
Carcinoid heart disease[1071, 1072]

Other Conditions

Paget s disease of the bone (p 231)[834]
Thoracic deformities (p 277)[574]
Myotonia dystrophica (p 421)[1231]
Friedreich s ataxia[834]
Primary arrhythmias (p 231)[834]
Traumatic heart disease[817]
Endocardial fibroelastosis (p 232)[834]
Congenital dilatation of the heart in adults[835]
Parchment heart[835b]
Familial cardiomegaly (p 416)[839]
Presbycardia (p 234)[848]
Myocardial sarcoidosis (p 235)[802]
Alveolar hypoventilation and congestive heart failure (pp 232 and 234)[840a]
Idiopathic myocardial failure occurring in the last trimester of pregnancy and in the puerperium (p 235)[842b]
Fat necrosis involving the parietal pericardial fat (p 253)[843b]
Gargoylism (p 235)[1232]

The observations which are set forth below may be of value in the analysis of unusual cases of actual or simulated heart failure Others have been made throughout the text particularly with reference to primary amyloidosis hemochromatosis beri beri, Wernicke s syndrome, the dys collagenoses, pericarditis, endocarditis, hyperthyroidism multiple pulmo-

when suggestive histologic changes of this condition are encountered in the right ventricle of a patient with cor pulmonale due to recurrent pulmonary emboli [777d]

10 It is generally agreed that there may be little clinical ground on which to differentiate *myocardial fibrosis* from constrictive pericarditis [851] This may apply even to the contours of the right ventricular and the right atrial pressure curves as determined by cardiac catheterization (i e , M shaped complexes in the right atrial pressure pattern, and an early diastolic dip and high end diastolic plateau in the right ventricular pattern) Nevertheless, it may be possible to make such a distinction hemodynamically on a quantitative basis In this regard reference is made to the following four findings which tend to suggest the presence of myocardial fibrosis (1) a right ventricular end diastolic pressure that is clearly less than one-third that of the systolic pressure, (2) a right atrial mean pressure that is well below 15 mm of mercury (3) the presence of a considerable respiratory variation in the mean atrial pressure or in the shape of the atrial pressure contour and (4) the descent of the right ventricular early diastolic dip below the baseline [851d]

11 Except as it relates to rheumatic fever diphtheria the rickettsioses endocarditis cardiomegaly in infants and the poststreptococcal states the clinical import of *myocarditis* has waned in recent years [836] In certain cases in which it is associated with cardiac hypertrophy a relentless downhill course is pursued with serious conduction defects, embolic phenomena and progressive heart failure characterizing the terminal illness More often than is probably realized the main difference between "chronic myocarditis and idiopathic cardiac hypertrophy depends upon the individual pathologist s definition and concept of the myocarditis process [145] Burchell has succinctly summarized the general experience as follows "Viral myocarditis as an entity is well established but certainly is a rarity difficult of exact etiologic substantiation, and difficult of assessment regarding the amount of histologic changes to correlate with the clinical picture [3]

12 In Central and South America, the problem of acute and chronic *Chagas' heart disease*—particularly their differentiation from rheumatic fever and coronary disease—is of greater importance than in the United States The heart is affected in the majority of patients with Chagas disease in the form of a diffuse severe specific nonvalvular myocarditis which leads to congestive heart failure and conduction or rhythm disturbances [837] Hepatomegaly splenomegaly various dermadromes, meningoencephalitis and other nonspecific signs and symptoms due to the infection with *Trypanosoma cruzi* are also observed

13 Although the significant incidence of *myocarditis and heart failure complicating acute glomerulonephritis* has been stressed both in the pathological and clinical literature—most notably by the virtue of their close association with hypertension—such a diagnosis is infrequently considered The explanation for this oversight stems from a number of factors These include the possible obscuring of the neck vein distention by the nephritic edema and the reluctance of clinicians to make this diagnosis when only a systolic apical murmur is present [838]

problem of *fatty infiltration of the heart* resulting in cardiomegaly, heart block, and congestive failure.[145] It is possible to diagnose this condition antemortem in the presence of a recent, rapid, and profound weight gain. This entity should not be mistaken for the visualization of the subepicardial fat which may not only be evident along the left border of the heart, but also on the right border.[1164b]

6. The combination of cyanosis, arterial hypoxia, and cardiac decompensation in an excessively obese individual may represent the effects of a secondary *"polycythemia of obesity,"* resulting from inadequate alveolar ventilation. On several occasions, this syndrome has actually suggested the diagnosis of congenital heart disease with a right-to-left shunt (p. 44).[149]

7. It is never superfluous to remind the clinician that an *active rheumatic carditis* must be considered in explaining the presence of congestive failure in rheumatic heart disease when other clear cut complications cannot be found. The sedimentation rate can be misleading in patients with high grade mitral stenosis who also have some element of failure, since it may be elevated in the absence of any evidence of active rheumatic fever.[836d] One might also consider the possibility of a *rheumatic pneumonitis* in the patient with rheumatic fever who is severely ill and exhibiting marked dyspnea and cyanosis. In fact, a primary acute pneumonitis may be the presenting feature of acute rheumatic fever.[8 3] Although there still exists much controversy over this entity, it must be entertained due to the salutory effects of corticotropin therapy.[8 2b]

8. The commonest causes of *cardiomegaly and electrocardiographic changes in young children without murmurs and with normal blood pressures* who have neither congenital nor rheumatic heart disease are subendocardial sclerosis[835] and idiopathic myocarditis.[836c] More rarely, glycogen storage disease of the heart,[8 90] medial necrosis of the coronary arteries, an aberrant left coronary artery[878f] and hyperthyroidism may be the cause of such myocardial disease.[838b] *Glycogenosis of the heart* is a rare disease of infants (p. 76). It may actually differ somewhat from the classical *von Gierke's disease*, especially with reference to the absence of a familial form of the latter disease.[829c, d] These children display feeding problems, muscular changes, neurologic abnormalities, macroglossia, and a general appearance reminiscent of hypothyroidism, mongolism, or the amyotonic states. The majority exhibit dyspnea, cyanosis, cardiomegaly, other evidences of heart failure, and usually succumb within their first year from this cause. The electrocardiographic findings are nonspecific. The diagnosis is further suggested by the finding of glycogen in skeletal muscle biopsies.

9. Many cases which were diagnosed in previous years as "idiopathic cardiac hypertrophy" were undoubtedly instances of *endomyocardial fibroelastosis* of the infantile, childhood, and adult types. As a result of the thickened endocardium, a situation is created that is analogous physiologically in many respects to that of chronic myocardial fibrosis and chronic constrictive pericarditis.[835] Mechanical insufficiency, impairment of conduction, or myocardial and vascular hypoxia occur, followed by a compensatory myocardial hypertrophy and dilatation, heart failure, coronary insufficiency, and thromboembolism. The right ventricle alone is rarely involved in endocardial fibroelastosis—a fact to be borne in mind

cyanosis that becomes worse during exercise but unaccompanied by respiratory distress an increased total arterial carbon dioxide content that persists despite acute hyperventilation, failure of the usual increase in minute ventilation during exercise, and the failure of carbon dioxide mixtures to augment ventilation are the clues to this diagnosis

22 The entity of *idiopathic myocardial failure occurring in the last trimester of pregnancy and in the puerperium* is not generally recognized and is usually misdiagnosed as a complication of either rheumatic or hypertensive heart disease[84b] It is initially characterized by left sided congestive failure, gallop rhythm, and generalized cardiac dilatation Chest and abdominal pain, embolic phenomena, acute hypertension, and T wave inversion may subsequently develop While no pathognomonic features are demonstrable pathologically, there are focal and diffuse areas of myocardial necrosis most prominent in the subendocardial portion of the ventricular wall Although two thirds of the reported patients appear to make complete clinical recoveries it is interesting to note that this disorder tends to recur with subsequent pregnancies

23 The heart is involved in one out of five patients with *sarcoidosis* who come to autopsy[60] The finding of any ancillary evidence for this disease in individuals with unexplained cardiomegaly, syncope, heart block, or other arrhythmias should direct the clinician s attention to the possibility of myocardial sarcoidosis

24 The cardiopathy in *primary systemic amyloidosis* (p 59) must be differentiated from *primary cardiac amyloidosis* in which the depositions of amyloid are localized to this organ It is not unlikely that the changes involving the proteins of the body fluids and tissues in elderly patients with the latter condition are the major factors determining the deposition of cardiovascular amyloid[8 9b]

25 While marked enlargement of the heart and heart failure are uncommon in patients with *cirrhosis of the liver* who do not have organic heart disease at the same time, there are a number of pathologic and deranged metabolic factors that could lead to these complications[8 9a] These include the following the cardiodynamic effects of the abnormal venous shunting between the portal and the systemic systems, the increased blood volume coincident with the extensive collateral circulation, the derangements of sodium and hormonal metabolism, and the effects of malnutrition multiple vitamin deficiencies hypoglycemia, and other disturbed metabolic activities on the function of the myocardium The significance of the large portacaval anastomoses and portapulmonary anastomoses that develop in patients with cirrhosis as related to the unsaturation of the arterial blood was discussed elsewhere (p 98) Some index of the caval venous hypertension or the increased azygos flow from the portal venous collaterals may be obtained if enlargement of the azygos vein shadow is noted in the chest films[345]

26 The subject of *gargoylism* (Hunter-Hurler disease) will be considered in a later chapter (p 421)[1 3] Three fourths of these individuals have significant cardiovascular disease of whom many die from congestive failure at the end of their first decade There is considerable involvement of

14 One should not be misled by a history of chronic asthmatic breathing in patients with emphysema or pulmonary fibrosis to the point of withholding cardiac therapy for decompensated *cor pulmonale* when there are reasonable grounds on which to base this diagnosis The circulation time has proved of some value in this decision The clinician should also reflect at great length if he contemplates withholding digitalis in these patients (as is practiced in some quarters) because of the purported reduction in pulmonary vascular perfusion and cardiac output as the myocardial efficiency improves [880b] This subject will be discussed later in this chapter (p 277)

15 While the validity of *Bernheim's syndrome* (right ventricular stenosis due to an eccentric left ventricular and interventricular septal hypertrophy) has been debated at great length, it still remains a useful clinical concept [839] In the presence of hypertensive heart disease or aortic stenosis, the signs of early predominant systemic venous engorgement and the absence of significant dyspnea should suggest this process [839c]

16 Similarly, the history of decreasing orthopnea in the presence of increased venous congestion is characteristic of *tricuspid stenosis* This diagnosis is commonly overlooked when other associated valvular defects are present On rare occasions, the alert diagnostician may be able to make the diagnosis of tricuspid occlusion resulting from a massive thrombus of the right atrium in the patient with rheumatic heart disease, hypertension or acute bacterial endocarditis This sequence of events might be suspected by the presence of a right-sided failure which is associated with the murmur of tricuspid stenosis or regurgitation, progressive dilatation of the right atrium, signs of obliteration of the vena cava and the presence of striking clinical variations within short periods of time [841] (Also see p 263)

17 *Atrophy of the heart* is a definite clinical and pathologic entity It occurs after prolonged illness, bedfastness, malnutrition or combinations of these factors [841a] When such individuals (especially inmates of concentration camps and during famines) are suddenly allowed greater activity and are subjected to overzealous refeeding hypertension and cardiac decompensation often ensue [841b c]

18 The precipitation of heart failure in elderly patients by the added load of various stresses (anemia thyrotoxicosis, infection) and in the absence of hypertension, valvular involvement or coronary disease might be accounted for by *senescence of the myocardium* ("presbycardia") [843]

19 The finding of a harsh continuous or diastolic heart murmur, and possibly cardiac hypertrophy or electrocardiographic changes, in an asymptomatic individual is consistent with the very unusual *arteriovenous fistula of the heart* [844] No therapy is indicated in most instances of this disorder

20 In patients with prostatic or mammary carcinoma who are receiving *large doses of estrogens*, it is well to bear in mind that the precipitation or aggravation of heart failure may actually be related more to this form of therapy than to cardiac metastases [1183]

21 The syndrome of *alveolar hypoventilation and congestive heart failure* in association with normal lungs and a normal chest bellows action has been described *as a result of impaired sensitivity of the respiratory center* to the normal chemical stimuli [842a] The presence of secondary polycythemia,

While a *pleural effusion* due to congestive heart failure is occasionally initially noted on the left side (perhaps resulting from the atypical conduction of the lymph through the thoracic duct rather than through the right lymphatic duct), such a finding should alert one to the possibility of a pulmonary infarction[83b] One should not overlook the possibility of a 'silent myocardial infarction in the presence of an unexplained pleural effusion in patients over the age of forty years There does not appear to be any one type of heart disease which leads to a predominant left hydrothorax when heart failure sets in Bilateral pleural effusions in the presence of a heart of normal size are rarely due primarily to congestive heart failure[83c] In these instances a most diligent search must be made for underlying metastatic neoplasms lymphomas, tuberculosis the various causes of polyserositis disturbances of water and electrolyte metabolism, and pulmonary embolization

The author is constantly impressed by the ability of certain cardiac patients to accumulate as much as 6 liters of *excessive fluid* and yet not manifest clinical edema Furthermore the "dry weight of the chronically ill cardiac patient may slowly decrease due to a progressive cachexia Accordingly, it is wise to bear this possibility in mind since unrecognized excesses of the extracellular fluid might be occurring even though the weight appears to remain steady

IMPORTANT CLUES IN CARDIAC PHYSICAL DIAGNOSIS

Among the notable salutory by products of the energies devoted in recent years to advanced electrocardiography vectorcardiography cardiac catheterization and surgery on the heart has been the unquestionable affirmation of the basic (and often definitive) value derived from the thoughtful and systematic clinical examination of the heart The consultant clinician who carries out his examination in an unhurried manner in a quiet well lighted room, and aided by a properly fitted stethoscope with both the bell and the diaphragm attachments, can frequently render a far wiser—and even more accurate—opinion than can the clinical physiologist There is much value in the use of mild sedation prior to the examination of young children with possible congenital malformations of the heart who are being referred for cardiac evaluation (Sedation is best achieved by the rectal administration of a rapidly acting barbiturate—6 mg per pound of body weight—dissolved in about 5 ml of water no more than 150 mg (or 2 5 grains) should be given however)

Many clues pertaining to the helpful aspects of cardiac physical diagnosis are included elsewhere in this chapter under the discussion of the various entities This is particularly true in the sections dealing with the diagnosis of multivalvular disease The reader is also referred to the admirable papers by Blake and Goodale Cassels Dressler et al, and the treatise by Levine and Harvey[83] A number of valuable points which the author considers to merit repeated emphasis will now be set forth Many of these are more exhaustively considered in the references just cited

1 A strong systolic thrust that is localized to the apex of the heart is probably the best single evidence of *left ventricular hypertrophy* There

the valves of the heart—chiefly the mitral valve—by nodular thickenings that are composed of gelatinous material

ATYPICAL MANIFESTATIONS OF HEART FAILURE

The clinician must also be constantly aware of the many atypical pulmonary and extrathoracic manners by which unrecognized heart failure may first manifest itself Four such features which repeatedly tend to direct attention away from the heart will first be mentioned—namely, *asthma hemoptysis, localized interlobar effusions* ("vanishing tumors of the lung")[63e] and *left vocal cord paralysis* In addition to mitral stenosis a variety of anatomic lesions can produce hoarseness as a result of compression of the left vocal cord (i e , arteriosclerotic heart disease, congenital heart disease, and aneurysms of the large vessels) [832d]

Many a chest specialist has been fooled by early congestive heart failure presenting as *a persistent and nonproductive cough* when the other manifestations of cardiac decompensation were not in evidence The aggravation of cough and dyspnea shortly after retiring, along with recent insomnia, may prove helpful to the alerted physician in this situation

It has been shown that the *distention of an aberrant azygos vein* can be an early objective feature of right sided heart failure [83a] Enlargement of the azygos vein shadow can also occur in patients with cirrhosis of the liver [245] In this instance such enlargement probably represents either the increased blood volume or the increased azygos flow from the portal venous collaterals or reflects the caval venous hypertension

It is important not to ascribe the *hepatogenic hypoglycemia* stemming from chronic passive congestion of the liver in heart failure to "cerebral anoxia" [61]

When convincing evidence of heart failure is lacking, the presence of an edema that affects the face and upper extremities and persists after rest should alert the clinician to other local vascular (venous and lymphatic) and systemic factors

Splenomegaly can occur in patients with rheumatic heart disease who have neither an endocarditis nor congestive failure [403b d] Similarly, *fever* may be present in patients with heart failure in the absence of an endocarditis or pulmonary disease [369, 403b f]

Another early manifestation of pulmonary congestion consists of an *insomnia during nocturnal recumbency* that promptly responds to diuretic therapy A true *psychosis* may make its appearance for the first time either during or after clinical heart failure [831] Such abnormal mental behavior must be differentiated from that resulting from the effects of certain therapies (*vide infra*) A true psychosis should be suspected when mental aberrations persist in spite of the absence or correction of any possible excessive drug administration and electrolyte derangements, especially in the face of a long history of marked personality difficulties

It has become increasingly clear as a result of a number of clinical studies that the *Cheyne Stokes breathing* noted in patients with heart disease usually implies previous cerebral injury It can be promptly dispelled by the inhalation of carbon dioxide

erable aid in clinically evaluating the hemodynamics within the right atrium, the tricuspid valve, and the right ventricle (The *a* wave represents atrial systole It is followed by a collapse of the full vein during early systole, and then by the *v* wave which represents the rising right atrial pressure caused by the systolic obstruction to the flow of blood by the closed tricuspid valve) Giant *a* waves are accordingly encountered when there are powerful right atrial contractions or increased resistance to filling of the right ventricle as might occur in pulmonary hypertension and tricuspid or pulmonary stenosis 'Cannon" *a* waves of very large proportions are also apt to be noted in patients with complete heart block They are due to the closure of the tricuspid valve at certain times when the right atrium is simultaneously contracting Prominent *v* waves are typically seen in tricuspid insufficiency (The clinician must be careful however, not to confuse a hyperactive carotid arterial pulse with large *a* waves)

5 The *hepatojugular reflux* can be a very helpful sign in both the diagnosis and treatment of congestive heart failure [833c] This phenomenon consists of the sustained distention of the neck veins following the application of pressure on the liver while the patient is in the semirecumbent position A good therapeutic effect with an increased cardiac output and venous return can be inferred by its diminution or disappearance following treatment

Burch has suggested that there be a quantitative control over the pressure and force applied to the hepatic area during the hepatojugular reflux test He has accordingly introduced the hepatojugularometer' (actually a flexible discoid rubber bag connected by rubber tubing to an aneroid type of manometer) for this purpose (A pressure of 50 mm of mercury—equivalent to a force of over 40 pounds—will usually raise the venous pressure in the presence of heart failure)[833j]

6 The *diminution of the carotid arterial pulse* may be of aid in establishing the presence of aortic stenosis or myocardial weakness

7 All cardiologists appreciate the great difficulties that may be encountered in defining slight degrees of *cyanosis* [83 b] This is particularly true in the case of infants and children The following list sets forth the relative frequency of the most common types of cyanotic congenital heart disease as encountered in a study of 139) patients with congenital malformations the tetralogy of Fallot complete transposition of the great vessels, pulmonary stenosis with atrial and ventricular septal defects the Eisenmenger complex tricuspid atresia persistent truncus arteriosus levocardia the Taussig Bing heart and anomalous drainage of all the pulmonary veins [877b] Cyanosis is usually not apparent in the first few months of life unless there is a very severe pulmonary stenosis or atresia [877b] The squatting and the anoxic attacks in the more severe cases are characteristic Cyanosis and clubbing of the toes—but not of the fingers—suggests a reversal of flow in a patent ductus arteriosus (p 286) (These observations are only of value however if the baby s skin is observed in the absence of crying) The cyanosis of the Eisenmenger complex typically becomes apparent around the age of puberty Two possibilities other than that of congenital heart disease which should be entertained in the presence of unexplained cyanosis in young children are pulmonary hemangiomas and methemoglobinemia

may also be a systolic retraction noted in the area just above and medial to the apex, resulting in a characteristic "rocking" apical impulse It is stressed that the apical impulse is *not* always palpable outside of the usually accepted normal outer limit Another generally shared erroneous belief is that an apex beat can be palpated in most normal individuals It can be felt only 25 per cent of the time if both sexes and all the age groups are taken into consideration (and even less prominently in the recumbent position) Dilatation in the absence of hypertrophy probably cannot account for the strong pulsation that is typical of hypertrophy If neither hypertension nor aortic valvular disease is associated with a mitral valvulitis of rheumatic etiology the finding of a heaving apical thrust should suggest a predominant mitral insufficiency When the mitral regurgitation is accompanied by a huge left atrium, there may also be a heaving pulsation over the right lateral chest wall

2 On the other hand *right ventricular hypertrophy* is characterized by a diffuse lifting impulse which is most prominent along the left sternal border This sign may be of great help in the presence of combined ventricular hypertrophy This heaving pulsation is more significant than an epigastric pulsation The latter may also be observed, but merely represents its more diffuse spread when marked right ventricular hypertrophy exists This particular pulsatory sign of the chest wall requires either a concomitant dilatation or the anterior placement of the heart by an enlarged left atrium In mitral stenosis, its magnitude is proportional to the degree of pulmonary artery hypertension

3 There are a number of *other important and potentially diagnostic pulsations of the chest wall* which the astute clinician can readily recognize by careful inspection and palpation [881] Brief reference will now be directed to several of the entities so represented

A *gallop rhythm* is frequently accompanied by a diastolic pulsation of the precordium, coinciding with the atrial contraction The concomitant reduction in the force of the systolic apical thrust the diastolic pulsation, and the tachycardia that is usually present produce a "tremor of the precordium

Although the balloon like bulge of the chest wall above or medial to the apex in a patient with a recent myocardial infarction is classically described as a *cardiac aneurysm*, one may be hard put to distinguish it from the pulsation of a hypertrophied left ventricle As healing and fibrosis of the infarcted area take place thus pulsation may disappear

Adhesive pericardial disease most often will produce a diffuse systolic depression of the precordium (i e both the ribs and the intercostal spaces), and then a brisk diastolic rebound The classical Broadbent s sign (a systolic tugging of the left thorax) is rarely observed and is actually not pathognomonic of this condition

There are three significant pulsatory findings that could direct the attention of the clinician to *tricuspid insufficiency* These consist of a diffuse systolic depression of the left hemithorax a heaving impulse over the lower half of the right anterior and lateral chest wall (especially valuable when an enlarged liver is not palpable), and a systolic expansion of the liver

4 Careful examination of the *jugular venous pulse* may be of consid

second sound, such is not the case with an opening snap, and (3) whereas no significant change will occur in the split second sound as a result of atrial fibrillation, the interval between the second sound and the opening snap will vary from one beat to the next—the longer the preceding diastole the later the opening snap will be heard It may disappear as the valve becomes more fibrosed and calcified

Opening snaps have also been recorded in patients with myxoma of the left atrium and with ruptured mitral chordae tendineae [854c] There should be little difficulty encountered in differentiating the opening mitral snap from a protodiastolic gallop The latter is most prominent at the apex, carries a much lower pitch and occurs later than does the opening snap

The spectral phonocardiographic studies of McKusick and his colleagues have admirably clarified the pathogenesis and clinical significance of *splitting of the heart sounds* [813e] They point out for example that striking inspiratory splitting of the heart sounds in patients over the age of forty with no other evidences of heart disease suggests respiratory disease

The slight asynchronous closure of the mitral and the tricuspid valves results in a *splitting of the first sound* over these particular valvular areas This is usually a normal variation and patients must accordingly not be rendered an organic diagnosis solely because of its presence

Similarly the *second heart sound in the pulmonary area is often normally split* (the first component representing closure of the aortic valve while the second element is primarily pulmonary in origin) A more pronounced splitting occurs during inspiration because of the delay in the second component that is produced by the increased right ventricular filling and the prolonged right ventricular systole Further divergence of the second basal sound will be encountered in the presence of a right bundle-branch block In fact when the competency of the right ventricle is questioned in a patient who has a right bundle-branch block one may gain a valuable clue concerning the former by noting the splitting of the second heart sound during inspiration Whereas wide splitting is heard when there is no heart failure (because of the delayed pulmonic valve closure) no such increase usually occurs when right ventricular failure exists [833b]

An atrial septal defect or mitral insufficiency can also be the cause of a markedly split second heart sound As the pulmonary vascular resistance increases in patients with pulmonary hypertension, there will be a narrower splitting of the second sound It is important not to confuse an opening snap caused by mitral stenosis with the second component of a split second sound (*vide supra*)

16 Much of the confusion concerning *protodiastolic and presystolic gallop rhythms* will be dispelled if it is realized that they occur at essentially the same time during the cardiac cycle as do the normal third and fourth heart sounds respectively While the protodiastolic gallop is one of the most important clues to the presence of heart failure, note must be taken of the fact that it also occurs commonly in mitral insufficiency (This can be explained by the rapid influx into the left ventricle during early diastole of the increased volume of blood that was confined within the left atrium) The clinician is also reminded that the finding of a presystolic gallop does

8. *Pulsus alternans* is often a valuable sign of myocardial weakness. It may not be apparent, however, unless the patient is examined in the erect or the semi-erect position.

9. The tendency for enlargement of the left atrium to take place posteriorly interferes with one's ability to diagnose this state solely by *percussion of the upper left border of the heart*. Such a maneuver, however, could reveal a marked enlargement of either the pulmonary artery or the aorta.

10. The value of *auscultation* will be enhanced if the examiner concentrates on each phase of the cardiac cycle over all the important areas of the heart, and if he will combine such an examination with both inspection and palpation. It is assumed that the reader is sufficiently versed in most phases of cardiac auscultation so as to justify the inclusion of only a few of the most salient observations that are pertinent to this text.

11. Levine and Harvey have stressed the caution required before attributing a "*poor*" *first heart sound* to weakness of the heart muscle when the second sound is normal.[33,36] In the presence of a regular rhythm, this finding might be indicative of an increased P-R interval. The importance of the variability of the first heart sound in the diagnosis of complete A-V block and of paroxysmal ventricular tachycardia is universally appreciated.

12. Much misinformation persists concerning the significance of the intensity of the sounds produced by *closure of the pulmonic valve* and the areas from which they are auscultated most clearly. In many instances, such closure is heard best in the *third* left intercostal space. Furthermore, one must be wary about attributing too much significance to a "P_2" that is louder than A_2, inasmuch as the closure of the aortic valve may actually be the major factor in the genesis of such an accentuated second sound.

13. A striking *accentuation of the first pulmonic sound* in the second left interspace (described as "the slatting sail sign" by Dow and Ahmurung) is regularly heard with slight (but not severe) pulmonic stenosis. This sign may prove helpful in the differentiation of this disorder from a functional murmur or an atrial septal defect.

14. An *accentuation of the second pulmonic sound* almost always occurs if an arteriovenous shunt is present (as might occur via a pulmonary vein, an auricular septal defect, a patent foramen primum, atrioventricularis communis, a ventricular septal defect, an aortic septal defect, an overriding pulmonary artery, a patent ductus arteriosus, or an arteriovenous aneurysm of either the coronary sinus or the lung).[37,38] The lung fields of infants afflicted in this manner may be misleadingly clear, notwithstanding the existence of a large shunt. A very clear second heart sound occurs most strikingly when the pulmonary artery is absent.

15. The importance of an *opening snap of the mitral valve* in establishing the diagnosis of mitral stenosis merits a brief discussion, particularly pertaining to its differentiation from other sounds with which it might be confused. The second component of the split second sound is most prone to give rise to such confusion. The following criteria may be used when this question arises: (1) whereas the split second sound is loudest at the pulmonic area (*vide supra*), the opening snap is most audible either to the right of the apex or at the left sternal border; (2) whereas respiration will effect a variation in the interval between the two components of the split

anomalous pulmonary veins venous hums (*vide infra*), a thyroid bruit dilated collaterals of the intercostal vessels in coarctation of the aorta (usually best heard posteriorly) postvalvular stenosis of one of the pulmonary artery branches (p 270) and the enlarged bronchial collaterals that develop in severe pulmonary stenosis or atresia (usually best heard over the right upper lobe bronchus) (p 287)

The presence of an atypical continuous murmur resulting from the rerouting of blood through the bronchial arteries may be of surgical significance, inasmuch as it raises the possibility of a complete absence of the pulmonary arteries [8,7] On the other hand there may be no continuous murmur when the pulmonary perfusion in pulmonary atresia occurs through a patent ductus arteriosus

19 In addition to their being obliterated by compression or motion of the neck *venous hums* also differ from the murmur of a patent ductus arteriosus in that the accentuation is diastolic rather than systolic [833f] While the auscultatory characteristics of venous hums may be quite variable (i e, rough, groaning musical or blowing), they can simulate true cardiac abnormality very closely The maximum intensity of these sounds in one or both of the supraclavicular fossae could prove to be quite helpful when doubt arises

POTENTIAL IATROGENIC HAZARDS IN THE MANAGEMENT OF HEART FAILURE

One of the clinical problems that confronts the consultant physician most frequently is the differentiation between symptoms that are due to heart failure *per se* and those directly resulting from the therapy which has been administered for this disorder This consideration is most apt to arise when symptoms persist or recur as the manifestations of the heart failure are abating or when apparent refractoriness to treatment develops A number of these possible iatrogenic complications will be presented briefly here Many are also discussed elsewhere in the text, as will be indicated The reader is referred to the more detailed analyses of this differential diagnosis by Orgain and Stead Blumgart and others [831] In addition, the succinct and provocative discussion by Altschule on the hazards associated with the treatment of cardiac decompensation is worthy of study [831c] These papers have served as valuable reference sources for much of the ensuing discussion

Cerebral Manifestations

1 A variety of cerebral symptoms (irritability personality changes depression, delirium) may be induced by the institution of *very strict low sodium diets* particularly in elderly patients whose kidneys are unable to conserve sodium

2 Similar central nervous system disturbances may result from *overdigitalization* although these are usually accompanied by other evidences of such overdosage (i e, visual symptoms gastrointestinal complaints arrhythmias)

not usually carry the serious connotations of a protodiastolic gallop, since it need not be associated with impending or actual heart failure

17 The important aspects of the various *murmurs* will be elaborated upon later in this chapter One must avoid the understandable tendency to equate the intensity of the murmur with its clinical significance On the one hand, very faint murmurs may be found in patients with severe mitral stenosis or pulmonary atresia On the other hand, a very loud systolic murmur could be produced by a small and relatively insignificant ventricular septal defect Similarly, the loudness of the pansystolic apical murmur of mitral insufficiency is frequently a poor indicator as to the amount of actual regurgitation Little issue can be taken with the dictum that a diastolic murmur practically always signifies serious heart disease It has been shown that the intensity level of the ambient background noise—particularly in hospital environments—constitutes one of the major factors in the ability or inability of physicians to hear heart murmurs [833g]

Pediatricians would do well to note routinely the presence of a heart murmur in early infancy since such information often later proves to be of great value [833k] This statement must be conditioned by the fact that loud murmurs are often transiently present at birth (because of the closing fetal channels and the relative stenosis imposed by the valves) Furthermore, a loud murmur can be auscultated one or two months after birth by the same physician who heard no murmur in the early neonatal period

The finding of a short, crescendo, grade II murmur with a buzzing or twanging quality at the third and fourth interspace along the left sternal border characterizes the functional murmur of infancy and early childhood In the presence of a more extensive murmur which cannot be readily localized, it may be virtually impossible to categorize it as either functional or pathologic except with the passage of time One should not overlook the various deformities of the chest in the genesis of pulmonic systolic murmurs, particularly kyphoscoliosis and severe funnel chest

Perhaps the most characteristic of all the congenital heart murmurs is that associated with a ventricular septal defect (the Roger murmur) This bruit is usually loud, coarse, rasping and accompanied by a palpable thrill over the third and fourth left interspaces When the defect is small, however the murmur may not be as coarse and no thrill may be palpable

The dictum that any significant and otherwise unexplained apical systolic murmur in a child over the age of four years should be regarded as rheumatic until shown to be otherwise is always valid

18 *Continuous heart murmurs* are most frequently associated with either a patent ductus arteriosus or an arteriovenous fistula The "machinery-like" murmur of a patent ductus arteriosus does not disappear when the jugular vein is compressed or when the neck is turned to the same side (as usually is the case when the murmur is caused by a venous hum)

It is well to bear in mind the following disorders that may produce murmurs or pseudomurmurs with which the above may be confused a ruptured sinus of Valsalva (p 297), a high ventricular septal defect with aortic insufficiency a coronary arteriovenous fistula (p 234), an aortic pulmonary window, a surgical shunt produced for the tetralogy of Fallot,

may not also exist This decision may be difficult to arrive at when it is not known for certain how much digitalis the patient has actually absorbed Furthermore, one must be aware of the possibility that arrhythmias are at times produced by the use of digitalis without the patient experiencing any gastrointestinal symptoms

2 In addition to the clinical features of digitalis toxicity the electrocardiogram may give some help in this regard by the following two signs (1) the duration of the Q T^c interval (i e an interval greater than 0 40 seconds probably excludes full digitalization), and (2) the finding of paroxysmal atrial tachycardia with block (due to the irritative effect upon the auricles) The abolition of this last mentioned arrhythmia or of a bigeminal rhythm following the administration of potassium therapy or after the withdrawal of digitalis generally will confirm the causative role of digitalis excess

3 Paroxysmal atrial tachycardia with block is not always due to digitalis overdosage, however In this instance the prognosis is not quite as serious particularly if no severe organic heart disease is apparent [831d] It may also be identified as a transient phenomenon while an auricular flutter or fibrillation is being converted "Regularization" of the ventricular response in digitalized patients with auricular fibrillation also suggests overdosage, even when there is an accelerated heart rate [831d] Should the strong vagal effect of digitalis slow the heart rate to less than 50 beats per minute in patients who have such severe myocardial disease or valvular stenosis that they are unable to significantly increase their cardiac stroke output, Stokes Adams attacks might be precipitated [831] When actual heart block and syncope are produced by digitalis intoxication the use of the external electric pacemaker and atropine may be lifesaving [831j]

4 The use of intravenous acetylstrophanthidin has been advocated as a pharmacologic test to detect digitalis overdosage (p 824) As a rule, this procedure is both impractical and hazardous for use by practicing physicians It is emphasized that electrocardiographic evidence of digitalis overdosage need not always be present when this state exists The reduction in the blood potassium that follows the oral or intravenous administration of carbohydrate can precipitate various ventricular arrhythmias in patients who are on the verge of clinical digitalis toxicity [300]

5 Brief mention is made of the encouraging reports pertaining to the use of an intravenous infusion of the disodium salt of ethylenediamine tetraacetic acid (Versenate), a chelating agent that binds and inactivates serum calcium, as a rapid treatment for digitalis toxicity The rationale of this therapy is predicated upon the synergistic relationship between digitalis and calcium [831h]

6 Most authorities appear to be agreed on the importance of gaining a good working experience with approximately three or four forms of digitalis to cope with the various situations in which their particular pharmacologic activities are most needed All agree that there is a much greater incidence of toxicity with the highly purified preparations than with the use of the whole leaf, especially in elderly patients and in the presence of an acute myocardial infarction On the other hand, another hazard in the management of digitalized cardiac patients is posed by the gradual de-

3 Cerebral symptoms commonly are the first evidence of excessive anticongestive therapy and the attendant *electrolyte disturbances*, especially when serious renal disease coexists These deranged metabolic states include hyponatremia, hypochloremia, alkalosis, acidosis, hypokalemia, and azotemia (*vide infra*)

4 The wide range of mental symptoms stemming from *hypoglycemia* is again stressed[61] The lowered blood sugar may be the result of the hepatic congestion, the diminished intake of carbohydrate, the excessive demand and utilization of this foodstuff, or any combination thereof

5 Confusional psychoses or coma may be the consequence of an induced *carbon dioxide narcosis* This state is most apt to complicate the use of high concentrations of oxygen in patients with emphysema and cor pulmonale (p 450)

6 Symptoms suggestive of increased intracranial pressure that develop in the patient who is receiving excessive fluids suggest the possibility of *water intoxication*[1309]

Gastrointestinal Manifestations

1 The *anorexia, nausea and vomiting* that result from the compression of the esophagus by a dilated left atrium from the reflexes stimulated by the passive congestion of the abdominal viscera, or from acute or chronic enlargement of the liver should be differentiated from (1) *excessive digitalization*, which is particularly prone to occur with rapid large dose therapy, especially in the elderly patient and (2) a wide range of electrolytic disturbances, most notably the *low salt syndrome* and *renal failure* Other commonly used drugs that might cause nausea and vomiting include ammonium chloride morphine, quinidine, and the xanthines

2 The clinician must always be on his guard for a *rectal impaction* when the congested bed-ridden cardiac patient does poorly and develops various gastrointestinal symptoms The author has encountered the symptom of *diarrhea* as a manifestation of congestive failure very infrequently It may occur as a digitalis effect, however[841e]

3 The presence of *jaundice* in the patient with an enlarged heart may be a result of concomitant liver disease pulmonary infarction, or prolonged *passive congestion of the liver*[326b] *This is particularly true* in instances of tricuspid stenosis (The ability of the liver to get its usual percentage of the reduced total cardiac output during congestive heart failure contrasts with the much greater disproportionate decrease in the renal blood flow)

Rhythm Disturbances and Digitalis Intoxication[831c d]

1 It is obvious that there may be a wide spectrum of abnormal rhythms associated with the various types of underlying cardiac disease that could lead to heart failure These arrhythmias can range from occasional premature systoles to ventricular tachycardias and all forms of heart block By virtue of the differences in the indicated therapy, however, one must attempt to define the presence of an excessive digitalis effect under these circumstances An associated depletion of potassium may or

disease with recurrent and prolonged bouts of previous heart failure They present themselves with intractable edema, reduced concentrations of sodium and chloride, progressive renal failure, and resistance to the mercurial diuretics

Levitt has ably reviewed the background of those therapeutic excesses which undoubtedly contribute to the development of this serious state [304c] An awareness of their implications in this regard could probably go a long way in minimizing the frequency of the low salt syndrome and its various biochemical components The latter ramifications include the following (1) hyponatremia with diminished total body sodium resulting from either cellular hypo-osmolarity or the excessive depletion of sodium, (2) hyponatremia with an intact total body sodium stemming from water intoxication and (3) hyponatremia with increased total body sodium as is encountered in such disorders as congestive heart failure, cirrhosis of the liver, and renal disease with the nephrotic syndrome that are characterized by the retention of sodium and water [304d] The dilution type of hyponatremia tends to be much more insidious in its clinical development than is the case with the clinical syndromes due to sodium depletion which are characterized by muscular cramps and an early shock like state One must be careful, however not to use clinical biochemistry as a wastebasket and attribute to hyponatremia other complications of congestive heart failure that are actually the result of renal failure pulmonary embolism, infection, myocardial infarction digitalis intoxication and unrecognized gastrointestinal bleeding resulting from the use of the anticoagulants

Several of these iatrogenic etiologic factors that contribute to the development of hyponatremic heart failure will be now set forth based to a large extent on the fine papers by Levitt Friedberg Schwartz and others [304]

Strict Salt Restriction The degree and the duration of strict salt restriction for cardiac patients is frequently carried out in an indiscriminate manner There can be little question that sodium restriction of at least moderate proportions is one of the major keystones in the therapy of congestive heart failure (Even when a hyponatremia exists in heart failure the total body sodium is still usually increased) Nevertheless to place *all* patients on a 200 mg sodium diet would be as logical as placing all heart patients on 0 1 gm of digitalis whole leaf daily There is little doubt that most cardiacs will fare very well on a sodium intake of 1 to 3 gm daily

One needs to be cognizant of reduction in the renal blood flow and the glomerular filtration rate as potential sequels to strict sodium restriction [304] In turn these effects could sufficiently reduce the renal function so as to preclude a salt diuresis Furthermore in the presence of profound sodium restriction the renal tubules will avidly reabsorb this ion with each dose of a diuretic tending to withdraw less sodium on the one hand and to exaggerate the loss of potassium on the other (*vide infra*)

One must bear in mind that while most of the serum sodium levels which are encountered in patients with congestive heart failure are either normal or low the vast majority of these individuals have already been treated with low sodium diets and diuretics In studies carried out by Iseri and his colleagues on untreated patients with congestive heart failure, the

digitalization of many of these individuals if this possibility is not anticipated and the weekly dosage modified accordingly. In cases of heart failure that appear to be refractory to therapy, the clinician is justified in pushing digitalis—even *to the point of mild toxicity, if necessary—to be assured* that complete digitalization is actually present. In the patient with pulmonocardiac failure who has marked oxygen unsaturation and carbon dioxide retention, digitalization might provoke marked toxicity and further deterioration of pulmonary function if concomitant measures directed to the underlying pulmonary disorder are not taken.[830b]

Gynecomastia may make its appearance for the first time during digitalis therapy. This effect is possibly related to the estrogenic activity of the digitalis aglycones.[1182] Although erythema multiforme has occurred shortly after the ingestion of either the digitalis whole leaf or digitoxin,[603b] the author is not aware of a drug fever that could be unequivocally demonstrated to be due to this important therapeutic substance. A number of instances of retrobulbar optic neuritis following the administration of various digitalis preparations are on record.[831i]

Electrolyte and Fluid Imbalances

There are many possible alterations in the metabolism of electrolytes that might account for a variety of cerebral, genitourinary and gastrointestinal signs and symptoms during the course of congestive heart failure. It is important to constantly re-evaluate the problem of the cardiac patient who is not doing well in an attempt to uncover and correct any treatable electrolytic derangements.[304] This is particularly true when liver or renal disease is present, when there has been considerable weight loss due to marked diureses, diarrhea, vomiting, or repeated thoracenteses, and when therapy has included a very rigid low sodium diet, ammonium chloride, excessive diuretics, ion exchangers, and carbonic anhydrase inhibitors. *One* is obviously aided considerably in this regard by being able to follow the concentrations in the blood (and occasionally in the urine) of sodium, potassium, chloride, calcium, carbon dioxide, and the nonprotein nitrogen.

Reference is made to the discussions in other sections of this book on *hypochloremic alkalosis* (p. 80), *sodium depletion* and *dilution hyponatremia* (p. 80), *hypokalemia* (p. 79), *hypocalcemia* and *tetany*,[831t] *ammonium intoxication* (p. 81), and *renal failure* (p. 50). If there is any question about the presence of a low chloride syndrome, it may be preferable to administer uncoated preparations of either ammonium chloride or potassium chloride in order to obviate the uncertainty of absorption that often attends the use of the enteric coated preparations. (The measurement of the urinary chloride output can readily confirm whether this is a factor in any patient who is given such therapy.) *Severe dehydration* can ensue in the edematous cardiac patient whose water intake has been severely curtailed.

While much still remains to be learned about the mechanisms involved in its pathogenesis, physicians and consultant cardiologists must be aware of the iatrogenic background leading up to the increasingly frequent state of *hyponatremic congestive heart failure*. The individuals who are *most prone* to this complication almost always exhibit long standing cardiovascular

filtration rate (in order to present an adequate electrolyte load to the kidneys) much harm can be done if this mode of treatment is pushed when the renal function is very poor. This state of affairs also might contribute to marked potassium depletion inasmuch as a more complete reabsorption of sodium is effected in the face of a reduced filtration rate, with the potassium loss thereby being augmented.

It is also pointed out that marked oliguria and azotemia can occasionally be induced by the severe dehydration following prolonged and copious diureses. The failure of the patient to achieve the expected diuresis with any of the diuretic agents should alert the physician to the possibility of impending fluid and electrolyte complications. The mercurial diuretics, in particular, must therefore be administered only as infrequently as appears to be necessary—preferably after the patient is primed with intermittent doses of either ammonium chloride or potassium chloride.

Potassium Depletion. The various roles exerted by potassium depletion in the genesis of the hyponatremic heart failure states are now receiving their due recognition. First, it is well known that there are reduced cellular potassium stores in practically all chronic illnesses. This also applies in the case of heart failure. For example the total body potassium has been shown to be decreased by radioisotope dilution technique measurements.[304f] Such depletion is often more accurately detected by the elevated plasma bicarbonate concentrations than by the levels of the serum potassium. The alkalosis may also represent a compensatory response to a marked diuresis induced by pochloremia.[304]

Second there is much evidence to support the belief that as potassium leaves the cells this ion is replaced by both hydrogen and sodium.[304g] Third the frequent use of the acidifying agents in cardiac therapy tends to reduce the plasma bicarbonate concentration while elevating the plasma potassium concentrations independently of other factors.[96] This might also obscure the presence of potassium depletion. Fourth the extracellular alkalosis associated with hypokalemia interferes with the chloruretic effect of the mercurial diuretics. It could accordingly account for some of the mercurial refractoriness. Fifth, potassium depletion tends to exaggerate digitalis intoxication which in turn can further depress renal function. Sixth potassium depletion and alkalosis are frequently associated with intensive thirst, notwithstanding the possible presence of considerable salt and water retention. As noted above, the consequences of such excessive water intake in the development of cellular hypotonicity can be considerable. Finally, reference is again made to the manner in which inadequate potassium intake marked sodium restriction and excessive diuresis can contribute to the hypokalemic state.

As mentioned in a previous chapter, one might expect to encounter potassium depletion when the cardiac patient who has been vigorously treated exhibits anorexia nausea marked muscular weakness, ileus, depressed tendon reflexes and drowsiness. Certain changes in the electrocardiogram that could be indicative of hypokalemia are depression of the ST segments inversion of the T waves and the presence of prominent or biphasic U waves.

serum sodium levels exceeded 150 mEq /L in many instances[2040] On the other hand, low serum sodium concentrations may reflect primarily the gravity of the cardiac situation, and bear but little reference to the effects of therapeutic measures Under these circumstances, one must exercise considerable reservation about administering *any* type of saline solution

It is further emphasized that the normal serum sodium concentrations may actually cover a range much wider than that hovering around 140 mEq /L On many occasions, one is apt to encounter a value of 130 mEq /L which does not appear to be related to symptoms, but rather represents a biochemical adjustment wherein the sodium metabolism is adjusted at a lower extracellular osmostatic level One cannot always use the status of the blood and urinary chlorides to indicate the behavior of the body sodium This is particularly germane when the patient is consuming chloride in combination with cations other than sodium

Over restriction or Forcing of Fluids Many physicians—according to their preference and previous teaching—tend to either over restrict fluids or force fluids in treating patients with heart failure These are factors which in themselves could contribute to the enhancement of severe hyponatremia and other electrolyte disturbances One indication of the magnitude of the fluid derangement in heart failure is that the extracellular fluid is usually at least twice its normal volume once overt edema is present[2040] Increasing thirst or weight (as determined on an ordinary bathroom scale) serve as two very important clues in averting the rapid accumulation of hypotonic edema Both call for a considerable reduction of the fluid intake and its careful titration so as not to exceed the urinary output by more than 500 ml (to make some allowance for the insensible perspiration)

Whereas the cardiac patient who is in mild failure and who has relatively good kidney function may actually be benefited by a liberal water intake, such is not the case in the edematous and hyponatremic individual The reduced concentrations of sodium and the other electrolytes tend to be lowered even further when the fluids ingested are hypotonic in comparison with the output, and when the intake of water is far in excess of the amount of urine excreted

Such a failure of water excretion in the presence of increasing hyponatremia can be explained by the following factors (1) renal disease, (2) reduced filtration rates secondary to both the heart failure and excessive salt restriction and (3) the ensuing inability to excrete electrolyte-free water (possibly in large measure related to a fairly complete inhibition of antidiuretic hormone secretion) Continuing interest will undoubtedly be directed to the role of secondary hyperaldosteronism as a factor in the renal retention of both sodium and water in patients with heart failure who are kept on very low sodium regimens[24]

Overzealous Use of Diuretics The overzealous use of the various diuretic drugs in order to achieve "dry weight has been so fervently advocated by a number of eminent lecturers that such a background for iatrogenic hyponatremia is not at all surprising Aside from water, most diuretic agents create a negative salt and water balance by imposing an unabsorbed osmotic load upon the renal tubules, thereby drawing these substances into the urine Since safe diuretic therapy demands a relatively normal

blood contains less basic reduced hemoglobin and the tissues accordingly retain carbon dioxide [831c]

Aminophylline Therapy While this agent is of great value in the management of bronchospasm, several untoward effects can take place These include the following gastrointestinal irritation, collapse (and even death) due to the vasodilatation resulting from its excessively rapid infusion, arrhythmias, and the development of anginal pain if the cardiac output is increased beyond the vascular capacity of the coronary system

Ammonium Chloride Therapy There is little doubt that this drug can (1) augment the diuresis produced by the mercurial diuretics, and (2) reduce the tendency to refractoriness of such diuretic therapy by preventing the development of marked hypochloremia A number of potential complications must always be kept in mind in patients who are receiving large amounts of ammonium chloride over prolonged periods, however, especially when there is impaired kidney or liver function or both These include ammonium intoxication (p 96) and severe acidosis The latter not only enhances the patient s dyspnea, but also can adversely affect the body s metabolic processes by depressing the utilization of carbohydrates and increasing protein wastage Ammonium chloride acidosis is characterized clinically by lassitude stupor, dyspnea of the Kussmaul type a marked hyperchloremia azotemia, and a low carbon dioxide combining power [306, 352]

Mercurial Diuretic Therapy These diuretics are practically indispensable to a number of individuals with severe degrees of heart failure The author has encountered many instances in which the failure to respond to such treatment was largely due to the injection of the drug into the buttocks and other edematous areas from which sites absorption took place with difficulty The diuresis may be enhanced if the mercurial diuretic is preceded and followed by twelve hours of bed rest [310] A copious diuresis in the elderly male with unrecognized prostatism not infrequently will result in acute distention of the bladder and urinary retention [194] The hemoconcentration and increased viscosity of the blood that follows a rapid and marked diuresis may lead to serious thromboembolic complications including cerebral thrombosis [772, 773] The cessation of a significant response to the mercurial diuretics is important to note since it can portend the low salt syndrome Furthermore toxic accumulations of the mercurials may occur if they are subsequently continued

In the patient with heart failure who is not fully digitalized, the sudden (but transient) hypervolemia that may follow the use of a mercurial diuretic can intensify the dyspnea and pulmonary congestion Attention is also directed to the following possible complications of these diuretic substances hypochloremia (p 80) the low sodium syndrome (p 246), hypokalemia (p 79) hypocalcemia and tetany,[831f] accentuation of digitalis intoxication by the hypokalemia and by the relative increase in the concentration of digitalis in the body [831d] and mercurialism especially when the oral mercurials are given in large amounts (p 68) Oral mercurial preparations are best administered on an intermittent schedule They should be avoided however when there is obvious severe renal disease present

It is pointed out that an erroneously high estimate of the plasma potassium concentration can be produced by hemolysis of the blood sample and delayed separation of the serum from the cells The level of the bicarbonate could lead the alerted clinician to suspect such an error

The Sequelae of Bed Rest

This moot subject is presented to de-emphasize some of the attitudes that have been adopted in recent years by consultant physicians concerning the supposed hazards of bed rest The belief that the development of phlebothrombosis in the veins of the lower extremities—and possibly subsequent pulmonary embolization—occurs primarily as a result of bed rest *is no longer accepted by all*[831c] *The extreme degrees of stasis that can be* the aftermath of oversedation, the excessive hemoconcentration stemming from overenthusiastic diuretic therapy, and certain changes in the coagulability of the blood caused either by drugs or by the outpouring of epinephrine and other hormones during heart failure and shock might be even more contributory The importance of orthostatic hypernatremia as this entity is related to the persistence of heart failure was cited earlier (p 231)

Other Potential Hazards in the Treatment of Heart Failure

Also see the section in this chapter dealing with the complications of treatment of myocardial infarction (p 273)

Morphine Therapy The potential untoward effects of this drug and the other opiates include the following excessive depression of respiration, particularly in the patient with cor pulmonale (p 278), gastrointestinal discomfort, severe itching, impairment of bladder function in patients with markedly enlarged prostate glands, the inhibition of mercurial diuresis,[831c] hypotension and collapse in the patient who is kept sitting or who is turned into the left lateral decubitus position (p 290),[1264a d f] and increased susceptibility to ventricular ectopic rhythms

Oxygen Therapy The physician must constantly check the manner in which oxygen is being administered to be sure that one of several rather uncommon complications is not occurring—in addition to the obvious local irritative effects and excessive warmth or coldness that can take place in an oxygen tent Reference is made to the following unrecognized atelectasis—a condition favored by the washing out of nitrogen in the pulmonary alveoli due to the breathing of high concentrations of oxygen (the nitrogen ordinarily tending to counteract collapse when secretions form), vasomotor collapse following the prolonged use of high concentrations of oxygen when the patient resumes breathing room air (due to the sudden withdrawal of the systemic vasoconstrictor effect of the oxygen) an increased tendency to ventricular fibrillation in the arteriosclerotic heart if marked differences in potential are induced,[1263r] carbon dioxide narcosis (p 450), and a reversible tissue acidosis The latter need not be related to the hypercarbia in patients with cor pulmonale It develops as a result of excessive carbon dioxide being dissolved in the plasma under the influence of high oxygen concentrations, with the consequence that the venous

There can be little doubt of the fact that *acute benign nonspecific pericarditis* presents itself to the clinician without an audible pericardial friction rub more frequently than is generally appreciated [847] In such instances, the physician must be guided by the description of the pain (aggravation by bodily motion and respiration), the fever the pleural involvement and pulmonary infiltrations (present in one half of these cases), the extensive changes in serial electrocardiograms, and the normal serum transaminase levels if he is to avoid making an erroneous diagnosis of acute coronary disease [45] The pain of acute pericarditis can be exaggerated by elevation of the pressure in a sphygmomanometer cuff or by the exertion of pressure on the epigastrium

When the necessity for differentiating this disorder from rheumatic fever arises, it is helpful to know that prolongation of the P R interval is encountered only very rarely in acute benign pericarditis The physician must be wary about a possible underlying acute myocardial infarction rather than an uncomplicated pericarditis when there are simultaneous elevations of the S T segments and inversion of the T waves

As larger batteries" of viral serologic studies become more available generally, there is little doubt that many more cases of acute benign pericarditis will be found to have a specific viral cause Thus pericarditis has already been described in instances of primary atypical pneumonia,[845] lymphogranuloma venereum,[557b] infectious mononucleosis [7 5d] mumps [568b] and the diseases caused by the Coxsackie viruses (Bornholm disease) [845b] Pericarditis is associated with a bacterial endocarditis only rarely, however [784b] An extraordinary incidence of acute benign pericarditis is encountered in children with Cooley s anemia who are subjected to splenectomy [5]

The persistence of a friction rub for prolonged periods should suggest causes for the pericarditis other than rheumatic fever These include tuberculosis malignancy disseminated lupus erythematosus polyarteritis and a chronic hemorrhagic pericardial effusion related to either coronary disease, anticoagulant therapy or the perforation of a mycotic aneurysm [440] Several instances of an irradiation pericarditis have been observed following radiation directed to the chest especially for carcinoma of the breast A chronic pericardial effusion may be caused solely by malignant hypertension Inhalation of talc dust from chronic exposure in a talc mill might be considered in the patient with a normal heart size, a negative tuberculin test, and long standing asymptomatic pericardial calcification who gives this occupational history [848]

Jackson Clagett and McDonald have reported three strikingly similar patients who were found to have *fat necrosis involving the parietal pericardial fat* at the time of surgery [848b] In each instance, acute low anterior chest pain was present, with a pleuritic component being experienced at some time The chest films revealed a mass close to the cardiac silhouette Serial electrocardiograms ruled out the existence of a myocardial infarction In view of the marked obesity in all these patients, this clinicopathologic entity might be diagnosed preoperatively—provided one can exclude pulmonary infarction primary or metastatic tumor a localized pleural effusion and a mesothelioma

Restricted Diets Mention was made earlier of the possibilities of inducing severe salt depletion in the patient who is concomitantly placed on a strict low sodium diet and intensive diuretic therapy One must also anticipate the development of other nutritional deficiencies under these circumstances, particularly those relating to hypoproteinemia, vitamin depletion and an iron deficiency type of anemia [130]

Abnormal Intake of Water The clinician runs the risk on the one hand of inducing *dehydration* in the patient with congestive failure if insufficient water is not consumed, while on the other hand also risking the possibility of *water intoxication* by forcing fluids The appearance of symptoms suggestive of increased intracranial pressure should lead one to suspect the latter disturbance (p 477)

Anticoagulant Therapy There are two types of complications to which reference in this discussion must be made These consist of (1) an excessive hypoprothrombinemia and bleeding when considerable engorgement of the liver is present, when the patient consumes very little food by mouth, or following antibiotic therapy, and (2) the occurrence of vascular thrombotic phenomena if the anticoagulants are suddenly discontinued [1276a] There appears to be an increased hypoprothrombinemic effect from dicoumarin when it is administered for the therapy of thromboembolic complications in patients with moderate to severe heart failure, even in the absence of significant liver enlargement [831b]

The use of Tourniquets and Venesection The use of these therapeutic techniques, which promptly relieve pulmonary congestion and edema, has undoubtedly saved many lives The prolonged use of tourniquets might induce the following sequelae excessive reduction of the cardiac output, contributing to the development of shock, the impairment of heat dispersal via the skin on the limbs distal to the site of the tourniquets leading to unexplained fever, the sudden onset of hyperpnea that takes place when the tourniquets are released (due to the sudden flooding of the system with large amounts of accumulated lactic acid and carbon dioxide)—which *must not be misconstrued as an indication for reapplying the tourniquets*, and the development of edema and thrombosis in the treated extremities [831c] Venesection likewise poses the possible hazard of precipitating vascular collapse if both the cardiac output and the blood volume are excessively reduced The performance of a phlebotomy may prove detrimental to the patient with cor pulmonale who has a secondary compensatory polycythemia [876a]

PERICARDITIS

Experience has repeatedly shown that pericarditis, both in its acute and chronic phases can be an elusive diagnostic problem In the case of acute idiopathic pericarditis, the abdominal pain (often accompanied by cramps, distention, tenderness spasm, nausea and vomiting) may be so alarming as to necessitate an exploratory laparotomy In fact, 5 of 13 patients in one series experienced significant abdominal distress as their chief complaint [845a]

constrictive pericarditis is primarily related to exertion—the occurrence of dyspnea at rest and orthopnea being rather infrequent because of the reduced right ventricular cardiac output which tends to preclude pulmonary hypertension

A final diagnosis of cirrhosis of the liver, congestive failure, chronic cor pulmonale peritoneal metastases thrombosis of the portal vein, the Budd Chiari syndrome thrombosis of the inferior vena cava, or Concato s disease deprives the patient of the salutory effects of a pericardiectomy [846, 850a] Even mitral stenosis can be simulated by the formation of localized fibrous bands that constrict the left atrioventricular groove

Hill and his colleagues have reported upon 16 cases of chronic constrictive pericarditis who presented themselves at the Mayo Clinic with previous diagnoses of primary hepatic disease, some of several years duration [846] The finding of "pure ascites" (abdominal fluid without edema of the legs), a normal liver biopsy, and protein values of more than 3 to 4 gm in the ascitic fluid should initiate a search for evidence of elevated venous pressure On the other hand, the clinician is reminded of the fact that passive congestion of the liver may in itself alter hepatic function [846b]

It must be further emphasized that the heart may be moderately enlarged in this disorder in up to one half of the patients, rather than being of the classical small and quiet variety Heinz and Abrams have emphasized the variable roentgenographic appearance of constrictive pericarditis [851] These authors believe that such observations as cardiac enlargement, cardiac pulsations within the normal range and the radiologic evidence of pulmonary artery and right ventricular enlargement *per se* should *not* be considered incompatible with constrictive pericarditis if the clinical picture of this disorder is very suggestive

Even though there may be a very thick pericardial fibrosis, calcification of the pericardium need not necessarily be present Furthermore, the existence of a severe and extensive bilateral calcific and constrictive pleuritis may be responsible for cor pulmonale without any significant involvement of either the pericardium or the mediastinal lymph nodes [876g]

Calcification was found in 17 of 35 patients with chronic constrictive pericarditis who were operated upon for this disorder at the Mayo Clinic [846] (The incidence of this sign in other series has been as low as 10 per cent and as high as 70 per cent) When calcification actually exists it is most commonly seen either high on the left border of the heart at or near the point of opposite pulsations along the sternal and diaphragmatic surfaces of the right ventricle or in the coronary sulcus between the left atrium and left ventricle While evidence of left atrial enlargement with a mitral configuration was also observed seven times in the Mayo Clinic report—presumably due to the constriction of the atrioventricular groove or of the left ventricle—pericardial calcification over the left atrium is quite infrequent Inasmuch as cardiac enlargement, pleural effusion and pulmonary vascular congestion of similar appearance can be encountered in constrictive pericarditis and in congestive heart failure from other causes the demonstration of these calcium deposits could prove to be very helpful

Only in recent years has the importance of the actual ventricular constriction been fully appreciated in the pathogenesis of this condition As a

There are a number of misconceptions about making the diagnosis of *pericardial tamponade* of an acute nature due to infection, tumor, hemorrhage, the "group" diseases, and "nonspecific" pericarditis, on the basis of physical signs Dyspnea was present in every one of 17 cases reported by Williams and Soutter, and frequently suggested congestive failure or primary pulmonary disease to the referring physician [849] These authors also cited the following fallacies which have been preserved and transmitted in *the form of clinical lore as being against this diagnosis*

The neck veins are not distended
The heart sounds are too good
The apex beat is too strong
The friction rub is too loud
No orthopnea is present
A falling venous pressure (terminal) or an insufficient rise in the venous pressure is observed
The pulmonary second sound is louder than the aortic sound
The ventricular pulsations on fluoroscopy are too good
The characteristic change in the heart shape by x ray with change in position is lacking

The importance of bearing these considerations in mind and of carefully observing and interpreting pulsating neck veins and a pulsus paradoxus (using the sphygmomanometer) is apparent from the ready relief that a pleuropericardial "window' can afford The defect in the pericardium should be made as wide as possible in view of the fact that some of these pericardial "windows" have closed, resulting in a reaccumulation of fluid

In contrast to the classic conception of *uremic pericarditis* as being a "dry process with only small amounts of pericardial fluid, it has been *shown that in up to one half of the patients with uremia* who have a pericarditis, the effusion amounts to more than 150 ml In one report of two cases, in fact, the hemorrhagic effusion measured 800 and 850 ml, which in turn produced a cardiac tamponade that represented the actual mode of death [177b] Furthermore, two cases of hemopericardium in chronic uremia that produced cardiac tamponade are already on record in which the diagnosis was made ante mortem, and in which striking clinical improvement followed removal of the pericardial fluid [17 c]

Cholesterol pericarditis is a very rare disorder (only 12 cases having been described to date) [848c] It is mentioned to point out the possible myx*edematous causation of this disorder, even though no* evidence for hypothyroidism could be found in many of these cases The association of a pericardial effusion with myxedema is better known [8]

Clinicians must also constantly be reminded of the fact that *constrictive pericarditis* can closely simulate the signs and symptoms of both cardiac disease of other origin and noncardiac disease Varying combinations of dyspnea, ascites, hepatomegaly, and edema—particularly in the absence of orthopnea, cardiac enlargement, pericardial calcification by tomography, and the other stigmata of previous tuberculous infection—may pose a diagnostic enigma While tricuspid stenosis may also present itself *with the peripheral manifestations* of congestive heart failure that are out of proportion to the amount of dyspnea being experienced by the patient, there are usually telltale murmurs present The dyspnea in chronic

cerning the effect of position, many of these patients experience an exacerbation of symptoms or actual fainting on bending forward They also have a definite preference for the right lateral decubitus position, in which the diastolic murmur may disappear

Unfortunately, the absence of a rheumatic history and the presence of the above features can also occur in mitral stenosis, with or without an associated ball valve thrombus There still exists some doubt as to whether myxoma of the heart represents a true neoplasm or merely a thrombus that has organized, and in the process has become degenerated and myxomatous In line with the latter concept a number of instances have been noted in which a chronic endocarditis with valvular thickening probably caused by rheumatic heart disease was concomitantly found [854b] The persistence of a loud first heart sound in the presence of auricular fibrillation and during the final stages of cardiac failure—even when murmurs cannot be heard—remains a most suggestive sign of rheumatic heart disease Another instance of the exception to every clinical rule however, is evidenced by the recording of an unequivocal opening mitral snap in the case of a myxoma of the left atrium [854]

Instead of simulating mitral stenosis a myxoma of the left atrium has also presented itself as coronary artery disease with myocardial infarction and progressive congestive failure [854d]

Other sources of diagnostic confusion in mitral stenosis include a *constricting collagenous mediastinal thickening* that obstructs the pulmonary venous return to the left atrium *constrictive pericarditis constrictive endocardial sclerosis, pectus excavatum other thoracic cage deformities,* the *verrucous endocarditis* of disseminated lupus erythematosus many *congenital deformities of the heart* (particularly atrial septal defects), and *healed bacterial endocarditis* [85] If one pays attention to the absence of pulmonary congestion and edema and the finding of tall spiked P waves, there will be less chance for confusing cor pulmonale with a mitral stenosis should a presystolic or protodiastolic right ventricular gallop be heard

Dilatation of the left ventricle from numerous causes can at times result in a *relative mitral stenosis* and may even produce the Austin Flint murmur *Thyrotoxicosis* has on repeated occasions simulated the clinical picture of mitral stenosis This is particularly true with reference to the accentuated first heart sound and the prominent pulmonary artery segment [40]

The occurrence of apparent Adams-Stokes seizures in the absence of frank heart block or arrhythmias should alert one to the diagnosis of a *ball valve thrombus of the left atrium* superimposed upon a rheumatic mitral stenosis [855a, b] The demonstration of calcification (particularly by tomography) either in the wall of the left atrium or in an organized thrombus adherent to the atrial endothelium is usually indicative of long standing mitral valvular disease with both stenosis and insufficiency Such a finding could prove of great value in certain instances of heart disease where the diagnosis is obscured either by the paucity of murmurs or by the age of the patient [853] A pedunculated ball thrombus has also been described on rare occasions in the right atrium[841] and in the hypertensive heart [855c]

result of the studies by Burwell and others, it has become clear that the major objective in the surgery for this disorder is the decortication and release of the two ventricles, rather than relieving the effects of the scars surrounding the atria and the great veins [851] The presence of diffuse myocardial fibrosis may not only mimic *all* the manifestations of constrictive pericarditis on the one hand, but can also complicate the latter disorder in which case even the most skillful resection will be of no avail (p 439)

It is not generally realized that there is ample clinical and experimental evidence to indicate a definite etiologic relationship between hemopericardium (due to anticoagulant therapy, operative trauma, infections, nonpenetrating chest wall injuries) and the subsequent development of constrictive pericarditis [850b, c] A hemopericardium has taken place after cardiotomy, necessitating aspiration and even re-operation Complete evacuation of the hemopericardium either by repeated pericardicenteses or by pericardiotomy, is mandatory to avert this complication

Rutledge and Foley have reported on two patients with chronic constrictive pericarditis in whom pure cultures of *Staphylococcus aureus* were obtained from localized collections of purulent material in the pericardium [850d] Others have also implicated the staphylococci, the pneumococcus and organisms other than the tubercle bacillus as the cause of constrictive pericarditis in a small percentage of cases

LESIONS SIMULATING MITRAL STENOSIS

Usually little difficulty is encountered in diagnosing the advanced and uncomplicated case of mitral stenosis There has been a tendency to over look the very important fact that the diastolic rumble of mitral stenosis often becomes evident *only* for several systoles as the patient is turned *into the left lateral position* following which it may quickly wane [833b] The *Austin Flint murmur* (due in large measure to the deflection of the anterior mitral leaflet by the regurgitant blood stream) can usually be differentiated from true organic mitral stenosis by the absence of a loud snapping first heart sound and by the absence of an audible opening mitral snap [833a] The problem of a 'relative mitral stenosis being produced by mitral insufficiency will be considered later in this chapter (p 262)

With the widening scope of cardiac and thoracic surgery, it is becoming increasingly important to make as accurate a cardiac diagnosis as circumstances will permit As a result of the emphasis upon valvular procedures, many capable observers have been impressed by the number of conditions that can organically or functionally simulate mitral stenosis [852] Several will now be considered

Myxoma of the left atrium may mimic mitral stenosis in every respect It should be suspected under the following circumstances (1) if the murmur is inconstant or variable, (2) if therapy with digitalis is ineffective, (3) if a rapidly progressive and severe decompensation appears, (4) if pain, edema *or dyspnea out of proportion to the degree of demonstrable* heart disease is present, and (5) if there are variations in either the murmur or the clinical status that are associated with a change of position [854] Con

may be produced The appearance of a murmur consistent with aortic stenosis that follows a recent myocardial infarction should alert the clinician to the possibility of a large mural thrombus in the left ventricle producing a functional aortic stenosis In this instance, the murmur is apt to change with position being most prominent while the patient is recumbent [863c] The paradoxic narrowing of the pulse pressure that is observed when congestive failure supervenes upon an underlying aortic insufficiency also merits brief comment This phenomenon is attributed to the replacement of the peripheral vasodilatation by vasoconstriction, under this situation, aortic stenosis may actually be simulated [863a]

When aortic valvular involvement is encountered in a female who gives no past history of rheumatic fever and where no evidence of other valvular involvement is to be found the diagnosis of a congenital bicuspid valve is suggested These valves are particularly prone to be affected by a bacterial endocarditis [4-0c] (Even the pathologist may encounter difficulty in differentiating between congenital and acquired bicuspid valves)

A number of interesting and unusual clinical features that tend to be associated with severe *aortic insufficiency* have been recognized in recent years particularly in those centers where surgical correction or amelioration of the defect by prostheses is being performed In this regard, Harvey Segal, and Hufnagel[864] have specifically called attention to the following observations

Sudden Death Sudden death is observed in 10 per cent of the patients regardless of the cause of the aortic regurgitation, and presumably due to a ventricular arrhythmia

Angina Pectoris Angina pectoris is present in one half of these patients, with the frequency being the same in the rheumatic group as in the syphilitic group When angina stems from aortic insufficiency, it tends to last longer, to occur at night and to exhibit a less dramatic response to nitroglycerine

Excessive Sweating While the severity of the sweating tends to parallel the clinical course of congestive failure it may be very distressing even before significant failure or angina are apparent In fact, the association of this complaint with systolic hypertension and heat intolerance could suggest hyperthyroidism It is also observed in patients with aortic stenosis but to a lesser degree

Neck Pain (Carotid Artery Pain) This symptom in all probability results from the excessive stretching of the carotid sheath

Abdominal Pain This discomfort is not the same as that associated with hepatic engorgement due to congestive heart failure but stems in large measure from the constant stretching of the wall or sheath of the abdominal aorta Numerous x ray studies and even laparotomies have been performed for peptic ulcer gallbladder disease pancreatitis or renal colic where this phenomenon was not appreciated

Splash Sounds Patients with free aortic regurgitation are apt to feel these sensations over the stomach or precordium They result from the pulsations of the enlarged left ventricle or aorta against the partially filled stomach

It was found in one recent large series of over 300 such cases of aortic insufficiency who were referred for surgical relief that the etiology is at

AORTIC VALVULAR DISEASE

Aortic stenosis may hardly seem to be a diagnostic problem on the surface, but experience teaches otherwise—particularly when considered in the light of a number of recent comprehensive surveys. The diagnosis was made correctly ante mortem in only 24 per cent and 57 per cent of 107 and 100 proved cases at several large teaching hospitals, respectively.[858]

Although congestive failure is the commonest manifestation, angina pectoris, dizziness, weakness, vertigo, and syncope may be the presenting symptoms. Impaired mental function (confusion, paranoia, stupor, convulsions, delirium) and weight loss which could not be accounted for by other causes are encountered relatively commonly.[858, 859] Syncope (unrelated to heart block) was found in 16 of 63 patients studied by Hammarsten, in 14 of whom it was precipitated by effort.[860] Patients with aortic stenosis who exhibit definite and persistent elevations of the basal metabolism rate without significant pulmonary congestion or dyspnea and in the presence of grossly and microscopically normal thyroid glands are not unusual.[861]

The right side of the heart can be the first to manifest failure clinically in this condition. For example, aortic stenosis may present itself as chronic cor pulmonale in the complete absence of any of the classical murmurs or signs of the valvular defect.[859c, 862] In this regard, it has been amply demonstrated that (1) the systolic thrill and murmur over the base of the heart are often absent (particularly in the presence of congestive failure), (2) the second aortic sound is frequently normal (particularly in the presence of hypertension), and (3) the pulse pressure may be normal or widened, *even when a severe aortic stenosis exists. Although the murmur of aortic stenosis* may be loudest at (or even confined to) the apex, its harshness and musical quality usually attest to its true origin. The systolic murmur of a ventricular septal defect is usually of a plateau type, is best heard in the third or fourth left interspace, and is poorly transmitted to the neck.

The demonstration of calcification in the aortic valve should not lead clinicians to exclude a rheumatic etiology. In fact, definite rheumatic lesions of the mitral valve are noted in one half of all patients with aortic stenosis.[859c] Brucellar endocarditis may not only resemble rheumatic fever, but can result in an aortic stenosis or mitral stenosis with calcification.

The chief shortcoming of direct arterial pressure tracings in the patient with aortic stenosis is that positive tracings frequently fail to distinguish between mild and severe obstruction at this valve. On the other hand, with the exception of certain individuals having combined mitral and aortic stenosis, *surgery for aortic stenosis is generally not indicated* if the gradient across the aortic valve is less than 40 mm. of mercury. (There are a number of limitations to the value of the brachial arterial pulse contour because of the numerous factors which bear upon the peripheral pressure pulse. Consequently, these tracings cannot be used conclusively either to rule in or rule out the diagnosis of severe aortic stenosis.)[859d]

It is already evident that the open technique, utilizing a heart-lung bypass and retrograde perfusion of the coronary sinus, affords the maximal surgical relief in aortic stenosis not only of the congenital type, but also in the face of extensive acquired calcification and deformity.[859c]

There are several circumstances in which a functional aortic stenosis

stenosis) Auscultation of a sharp first heart sound and an opening snap at the mitral area are all the more helpful in the diagnosis of mitral valvular disease when it is realized that certain patients with severe stenosis may have either slight or no diastolic murmurs, and that others with free insufficiency may exhibit loud diastolic murmurs (usually early in their timing, however)

Experience has pointed out that when heavy calcification of one valve (a sign best demonstrated by tomography) is found, there is usually organic involvement of at least a second one [855b] On the other hand the presence of many murmurs *per se* does not rule out the possible salutary effect of surgery This is especially true when predominant stenosis of either one or both valves is revealed by pressure studies in a patient with double aortic and mitral murmurs

Reference was already made to the possible difficulties encountered in diagnosing *aortic stenosis* especially when considered in light of the fact that the intensity of the murmur and thrill are at times of little value in determining the severity of the stenotic process This is particularly true in the presence of heart failure or hypertension Dexter and his associates have been impressed by the readiness with which aortic stenosis can mask the characteristics of a *concomitant mitral stenosis* They call attention to the potential value of brachial arterial pressure tracings and the demonstration of left ventricular hypertrophy by electrocardiogram in this differentiation [856a] Determination of the pressure gradient across the aortic valve by left heart catheterization performed simultaneously with right sided catheterization to ascertain the cardiac output by the Fick principle has largely reduced the necessity for diagnostic exploration of the aortic valve [856] The presence of auricular fibrillation in a patient with aortic stenosis should also cause one to suspect a coexisting mitral stenosis

Mention is made of the profound cardiac decompensation that can follow a mitral commissurotomy in the presence of concomitant and unaltered aortic valvular disease [856b] This valve should therefore be attacked prior to the mitral one in the presence of combined valvular stenosis

The combination of *mitral stenosis and aortic insufficiency* is rather uncommon It should be suspected in patients (particularly women) with clinical evidences of the latter disorder who also are found to have auricular fibrillation, a loud opening mitral snap hemoptysis and displacement of the esophagus Some difficulty may be encountered in evaluating whether the early diastolic murmur that is heard in about one third of patients coming to mitral valve surgery as a high pitched blowing murmur of low intensity along the left sternal border represents functional pulmonary insufficiency (the Graham Steell murmur) or actual aortic valvular involvement [833, 857] In the case of the former however there is usually an obvious dilatation of the pulmonary artery and a diminution of the murmur postoperatively (The intensity of the second pulmonic sound is not always a reliable guide to the degree of pulmonary hypertension) Accordingly, inasmuch as the murmurs of aortic and pulmonic regurgitation might be difficult to distinguish one must pay considerable attention to the level of the resting diastolic pressure A level of 50 mm of mercury or less tends to confirm the presence of significant aortic regurgitation [856]

present predominantly rheumatic (83 per cent), with syphilis representing only 12 per cent of the cases encountered, and congenital disorders (Marfan's syndrome, bicuspid aortic valve, coarctation of the aorta) accounting for 4 per cent The association of aortic regurgitation with rheumatoid spondylitis (*vide infra*) was noted in five patients It is pointed out that the femoral pulses can be normal or even accentuated when there is an associated coarctation of the aorta In such an instance, the demonstration that the radial pulses are stronger than the femoral pulses might lead to the correct diagnosis This is no longer an academic consideration, inasmuch as the coarctation can be repaired at the same operation during which the plastic valve is inserted [864]

When *aortic stenosis and insufficiency coexist*, some of the signs of one lesion can intensify those of the other (as the intensity of the thrills and murmurs of stenosis) while others may be cancelled (as the aforementioned blood pressure findings) [863b] In view of the increasing emphasis upon aortic valve surgery, the determination of the heart size along with a study of both the left heart pressures (by direct catheterization) and the carotid pulse, are of great help in indicating which type of lesion predominates [853c] Since the usually rough systolic murmur of a severe isolated stenosis may be very faint if a low cardiac output is present, and since no electrocardiographic abnormalities occur in up to 15 per cent of such patients, these observations can prove to be most rewarding It is pointed out that the murmurs of both pulmonary insufficiency and of aortic insufficiency may sound very much alike, and that they may be heard loudest in the same areas along the left sternal border [833a]

The treponemal immobilization test has been demonstrated to be of great value in establishing the diagnosis of syphilis in patients with lesions of the aorta or the aortic valve in whom the standard serologic tests for syphilis were either nonreactive or weakly reactive [855e] This is also true in a negative sense in the case of the severe aortic insufficiency that occasionally accompanies rheumatoid spondylitis which can closely simulate the aortic valvulitis produced by syphilis [876] A more detailed description of this entity may be found under Group X (p 312)

SOME IMPORTANT ASPECTS OF MULTIVALVULAR DISEASE

It has become increasingly apparent with the ever increasing emphasis upon the surgical correction of mitral and aortic valvular stenosis that considerable preoperative attention must be actively paid to the possible presence of multivalvular disease Since unrecognized multivalvular pathologic conditions can have considerable bearing upon postoperative morbidity in these cases, a brief review of some of the more important considerations relating to this problem will be now set forth

The definitive importance of certain features of the careful cardiac examination in defining multivalvular defects even when fluoroscopy and cardiac catheterization have given inconclusive results, has been asserted (pp 237–243) In this regard, reference is made to the sternal heave (right ventricular hypertrophy), the localized apical heave (left ventricular hypertrophy), and the opening mitral snap (usually indicative of mitral

The frequency with which the effects of mitral regurgitation are observed roentgenographically six months or longer following a mitral valvuloplasty has been emphasized by Soloff and Zatuchni [857b] (They attribute part of this cardiac enlargement to an intensification or reactivation of the rheumatic carditis) Otto and his colleagues have pointed out the unpredictable changes in the apical systolic murmurs occurring postoperatively and their poor correlation with the surgeon s impression of the residual anatomic defect [857] The vexing problem of "recurrent mitral stenosis will be discussed in detail in Group XV (p 441)

Instances of *coexisting mitral stenosis and pulmonic stenosis* demonstrable on cardiac catheterization are rare, but have been described [856e]

The occurrence of *concomitant tricuspid stenosis and mitral stenosis* is not at all rare The cardiac surgeon must be made aware of this combination preoperatively inasmuch as he should be prepared to widen the tricuspid valve immediately after the mitral valvuloplasty If this is not *performed, the manifestations of the tricuspid disease will be precipitously* increased following the mitral valvuloplasty [865] The right sided approach to mitral commissurotomy has the added advantage of enabling the surgeon to both diagnose and relieve marked coexistent tricuspid disesae at the same procedure Utilizing this right atrial approach to the mitral valve, Bailey and Morse encountered 19 instances of tricuspid stenosis (unsuspected in 14 cases) and 9 instances of tricuspid insufficiency (unsuspected in 7 cases) among 170 patients with mitral stenosis [865b]

During cardiac catheterization the demonstration of an elevated mean pressure gradient from the right atrium to the right ventricle during ventricular diastole, which widens with exercise is diagnostic [865d] In addition to the presence of right sided failure and the characteristic findings on cardiac catheterization the clinician might be made cognizant of tricuspid stenosis by the presence of systolic or diastolic murmurs that are heard loudest over the lower sternal area (especially on inspiration), and by presystolic liver or jugular pulsations (not diagnostic, however) The murmur of tricuspid stenosis is accentuated in the right lateral position, whereas that of mitral stenosis is diminished by this maneuver The accentuation of the murmur of tricuspid stenosis during inspiration (Carvalho s sign) is of considerable diagnostic importance and is a reflection of the increase in gradient and flow over this valve that takes place with inspiration [865d] The opening snap of a stenosed tricuspid valve has been heard in the area of the xiphisternum and for several centimeters downward and to the right

There may be a relative tricuspid stenosis due to the asymmetric commissural fusion and "tight bowstring' orifice occlusion produced by the atrial enlargement This might disappear following a valvuloplasty in which the pulmonary hypertension is relieved [865d] It is also pointed out that one might encounter the diastolic rumble of a right sided Austin Flint murmur in the presence of a relative tricuspid stenosis in patients with very large right ventricles This may be the case in cor pulmonale resulting from multiple pulmonary embolization, and could lead to considerable diagnostic confusion if the diagnosis of mitral stenosis is made [777d]

Several instances have been reported in which a proved tight mitral stenosis and a concomitant tricuspid stenosis were associated with normal

While some degree of *mitral regurgitation* usually accompanies *mitral stenosis*, severe mitral regurgitation and severe mitral stenosis are generally incompatible, particularly when the mitral valve area is calculated to be less than 1 0 sq cm One should suspect the presence of significant regurgitation in patients with mitral stenosis when either right ventricular hypertrophy is absent or if left ventricular predominance is found electrocardiographically, and by the lack of radiographic prominence of the pulmonary artery Not only will these patients not be benefited by surgery (at the present time), but they are frequently quite intolerant of anesthesia Significant mitral insufficiency probably does not exist preoperatively in the absence of an apical systolic murmur

A "relative" mitral stenosis can be paradoxically produced by a marked mitral regurgitation Such a dynamic effect stems from the large forward flow across this valve that occurs during early diastole as a result of the very large regurgitant flow during the previous systole [833a] In this situation, early loud apical diastolic murmurs and an opening mitral snap may also be heard for the reasons just cited Furthermore, there are occasional instances wherein mitral insufficiency exists as the only valvular lesion, yet in which the features of right ventricular hypertrophy are found, both by x-ray and electrocardiographically

The presence of a calcified mitral valve should alert the clinician to the presence of significant mitral insufficiency, however, this is not in itself a contraindication to surgery The systolic expansion of the left atrium and the other fluoroscopic signs that are considered suggestive of mitral insufficiency have shown poor correlation with the surgeon's impression of the regurgitant jet at the time of surgery Other general clues to the differentiation of predominant mitral valvular involvement that may be demonstrated in good chest films include the following in mitral insufficiency, there is more apt to be huge dilatation of the left atrium a broad sweep of the esophagus, and marked left ventricular enlargement, in mitral stenosis one is more likely to see the evidences of pulmonary vascular hypertension (dilatation of the main pulmonary artery and its proximal branches), vasoconstriction or normal sized vessels in the peripheral lung fields and evidences of pulmonary lymphatic congestion and increased intercellular fluid (Kerley's "septal lines, blurring of vessels, prominent fissures) [83 b]

An attempt should be made to distinguish valvular calcification from calcification either in the wall of the left atrium or in an organized thrombus which is adherent to the atrial endothelium As previously indicated the latter is indicative of long-standing mitral stenosis and insufficiency [853]

The clinician must be careful not to misinterpret the systolic murmur of tricuspid incompetence for that of mitral insufficiency in a patient with mitral stenosis, and accordingly minimize the potential value of surgery While the murmur of tricuspid insufficiency may also be heard over the mitral area, it tends to increase with inspiration This contrasts with the tendency of the murmur of mitral insufficiency to decrease with inspiration [833b] When the question arises as to whether a given patient has tricuspid or mitral insufficiency, the latter probability is suggested by the finding of a prominent third heart sound

the upper abdomen" because of its ability to simulate pathologic conditions affecting many organs in either the upper abdomen or the lower thorax.[13, 8] There are three main potential sources of error that might lead the clinician to make the diagnosis of true angina pectoris in patients whose primary difficulty is actually that of a hiatal hernia. These are (1) patients with hiatal hernia and other forms of esophageal dyskinesia can exhibit a good response to nitroglycerine which may be misleading, (2) the discomfort in both coronary insufficiency and hiatal hernia can be induced by the combination of overeating and recumbency, and (3) the ruling out of this diagnosis on the basis of one negative upper gastrointestinal x-ray study could be premature. Many clinicians have encountered the problem of the patient with a diaphragmatic hernia which simulated angina pectoris in whom the hernia could not be demonstrated on one examination (which included the Trendelenburg position) but in whom this abnormality could be readily detected the next time. Even with repeated studies and the use of multiple positions and techniques it is possible to demonstrate only 85 per cent of these herniations, inasmuch as they are frequently intermittent affairs that tend to reduce themselves spontaneously.

The *high splenic flexure syndrome* is another benign subdiaphragmatic entity that can be misdiagnosed as angina.[866b] Evacuation of the bowel and the assumption of the knee-chest position may relieve the lower left chest discomfort in this condition.[866b]

An additional aerophagic syndrome which may result in pseudoangina is due to the accumulation of air in the stomach—the so-called *magenblase syndrome*. The "phrenic reflex" probably explains the anginoid distress in the chest during the early postprandial period. Roth and Bockus have further pointed out that not only may angina provoke aerophagia and a subsequent magenblase as a result of the engendered anxiety but that the enlarged magenblase can actually mechanically aggravate an existing coronary insufficiency.[867f]

Mention must be made of *mediastinal emphysema* and *pneumothorax* in the diagnosis of acute chest pain, inasmuch as they both can produce substernal distress with radiation to the neck, back, left shoulder, and arm and may be overlooked in their minor forms. The value of Hamman's sign is well established in the former disorder. It is not generally appreciated, however, that this feature also might be a manifestation of a small left-sided pneumothorax.[868] For example, in one review of 98 cases diagnosed as spontaneous mediastinal emphysema at the Johns Hopkins Hospital a left pneumothorax was observed in 48 instances and a right pneumothorax in four. Only the presence of subcutaneous air or the unequivocal demonstration of air in the mediastinum or subcutaneous tissues of the chest or neck by x-ray are pathognomonic of mediastinal emphysema. (One cannot rely upon the finding of a translucent zone along the left cardiac border as evidence of air in the mediastinum since it may also be found when air is trapped between the visceral and parietal pleura.) In such situations, the symptom of dysphagia is helpful in pointing to a mediastinal emphysema.

Particular note is made of the frequency with which the local tender-

pulmonary artery and "pulmonary capillary" pressures at cardiac catheterization[865c] This points out the fact that mitral stenosis cannot be completely ruled out clinically in the patient with obvious tricuspid stenosis who presents himself for surgical correction, even with the finding of normal "pulmonary capillary"—pulmonary artery pressures and a left atrium of normal proportions As previously indicated, the increasing experience with direct left sided catheterization holds much promise of aid in many of these unusual instances of masked multivalvular disease[856c]

DIFFERENTIAL DIAGNOSIS OF MYOCARDIAL ISCHEMIA

No attempt will be made to review comprehensively the complete differential diagnosis of chest and cardiac pain The reader is referred to a number of fine papers in which the differential diagnosis of pain in the chest is exhaustively considered[866]

It will suffice for the present discussion to recall that disorders of the chest cage (including the ribs, vertebrae, skin, sternum, and muscle), the intercostal or cervical nerves and their roots, the lungs, the pleura, the esophagus the mediastinum, the gastrointestinal tract, and neurocirculatory asthenia may simulate or coexist with coronary pain For example, primary or metastatic malignant tumors of the mediastinum are often associated with considerable chest pain (p 336) Also the pre-eruptive phase of herpes zoster may last for as long as four days One clue to its possible presence is the burning character of the pain

There is altogether too much emphasis currently being placed upon minor variations of the T waves and slight depression of the S T segments (especially at the junction) following exercise as being indicative of coronary heart disease On the other hand the reverse type of clinical situation often holds true—namely true coronary disease being mistaken for disorders of these aforementioned organs

Not only must the nature of the discomfort (this description often being more appropriate than that of actual pain) and its location be ascertained in detail but also its relationship to various precipitating factors—either singly or in combination The author has found it very helpful for purposes of orientation to bear in mind that even though true angina pectoris may occur in atypical locations, it always tends to recur at the same site in that individual *One should also be aware of the fact that the relief of chest pain which is afforded by rest is characteristic of true angina only when the episodes are chiefly precipitated by effort*

One of the most reliable objective diagnostic criteria for coronary pain of the anginoid type is the ability of glyceryl trinitrite to increase the patient s exercise tolerance by a considerable margin It is cautioned that there may be considerable risk involved in attempting to demonstrate a diagnostic pathologic response to either exercise or hypoxia in the patient s electrocardiogram when the chest pain has been present for only one or several weeks (All cardiologists of experience have had the sobering experience of observing the development of a myocardial infarction in patients with long standing neurocirculatory asthenia)

Esophageal hiatal hernia has been designated as "the masquerader of

Another potential pitfall relating to the misinterpretation of a laboratory procedure that is coming into increasing prominence as an aid in the diagnosis of acute coronary disorders is to be found in the serum transaminase Aside from such obvious causes of elevation of the activity of this enzyme (*as liver disease and muscle injury elsewhere in the body*) (p 694), the opiates *per se* can induce such increases [869d] This would appear to be due chiefly to the acute spasm of the duodenum and the biliary tract which these drugs can produce

Serious consideration to a variety of *nonatheromatous and uncommon causes of myocardial ischemia* might be entertained when the disease complex is quite atypical Such an approach is warranted here if only on the basis of the alarmingly high incidence of this type of heart disease in our society which *per se* might mislead the physician For example the rarity of coronary embolism (even in endocarditis) and the predilection for its occurrence in the left coronary vessels account for its usually being mistaken *for coronary thrombosis* [784] *Also typical anginal pain can be associated* with right ventricular hypertrophy and ischemia as occurs in isolated pulmonic valvular stenosis [866c] Surgical correction in these instances of ' right sided ' angina affords complete relief

The following listing of the nonatheromatous causes of myocardial ischemia has been modified after that proposed by Edwards [869]

1 *Altered dynamics associated with aortic valvular disease*
   - Aortic stenosis (p 258)
   - Subaortic stenosis
   - Aortic insufficiency (p 259)
     - Luetic
     - Bacterial endocarditis
   - Incomplete dissecting aneurysm (p 295)
     - Spontaneous
     - Traumatic
   - Marfan s syndrome (p 267)
   - Congenital ventricular septal defect
   - Aneurysm of an aortic sinus (Valsalva) (p 297)

2 *Anatomic coronary ostial narrowing*
   - Syphilitic aortitis
   - Primary arteritis of the aorta (pulseless disease) (p 301)
   - Dissecting aortic aneurysm (an uncommon manifestation) (p 295)
   - Postaortic valvulotomy

3 *Coronary embolism* (p 211)
   - Rheumatic mitral valvular disease
   - *Bacterial endocarditis*
   - Tumor emboli
   - Fat emboli
   - Intracardiac mural thrombi
   - Myxoma of the left atrium (p 256)
   - Thrombi from pulmonary veins
   - Thrombi from peripheral veins (paradoxical embolism)
   - Embolus of atheromatous material in the coronary artery

4 *Congenital diseases of the coronary arteries*
   - Anomalous origin of the right coronary artery
   - Anomalous origin of the left coronary artery
   - Coronary arteriovenous fistula (may produce a continuous murmur) (p 234)

5 *Manifestations of systemic disease*
   - Hypertension (nonatheromatous thickening of the media and intima)

ness resulting from swelling or irritation of the upper costal cartilages (*Tietze's syndrome*), the xiphoid, or the ribs and adjacent structures in the region of the left breast is mistaken for cardiac, pleural, or intercostal nerve pain [867, 1157] The so-called *precordial catch* can result in severe left sided chest pain [867a] It probably represents the pinching of the affected intercostal nerves by poor posture, most notably as produced by the slouched position The importance of promptly recognizing and treating the musculoskeletal chest pain that develops in the postmyocardial infarction period is emphasized

Manubriosternal arthralgia is another distinct chest wall syndrome that can be readily mistaken for angina by virtue of the location of the abbreviated attacks of chest pain and their relationship to movement The discomfort is clearly localized at the manubriosternal joint, however, and is at times associated with a definite clicking sensation in this area [868d] Attention is also directed to the simulation of angina pectoris by the *radiculitis* resulting from an osteoarthritis of the cervicodorsal spine, by a ruptured intervertebral disc in the lower cervical region,[868] and by neurovascular changes secondary to the sleeping posture (the hyperabduction syndrome) [868c]

It is almost superfluous to emphasize to the clinician consulting this text the primary atheromatous basis of angina pectoris in the vast majority of cases Nevertheless when coronary disease occurs in young individuals (particularly females) and in the absence of significant hypertension or obesity the possibility of hypercholesterolemia, xanthomatosis, gout diabetes mellitus chronic nephritis impaired ovarian function hypothyroidism or some other *underlying deranged metabolic state* must also be considered

Furthermore the clinician should make every effort to rule out an underlying cardiac or noncardiac mechanism that is triggering recurrent attacks of angina pectoris These possibilities include spontaneous hypoglycemia hyperthyroidism, pulmonary embolism (p 212), and early left ventricular failure The last is of notable importance in the patient who is experiencing nocturnal status anginosus especially while in the decubitus position [869b] Although angina decubitus was originally described in young patients with aortic insufficiency it can occur in coronary artery disease where no valvular involvement is present In contrast to the pale, cold facies encountered during angina of effort the face is often warm and flushed during angina decubitus

One diagnostic pitfall leading to an erroneous diagnosis of acute myocardial infarction which the author has encountered on a number of occasions is found in *the post tachycardia syndrome* (i e , the transient inversion of T waves in the electrocardiogram following a bout of paroxysmal rapid heart action) This is particularly true in the case of paroxysmal auricular tachycardia, a frequent arrhythmia in which the patient s symptoms might suggest an acute coronary insult [869c] The short duration of this electrocardiographic abnormality—along with the absence of other positive findings in the electrocardiogram the chest films the ballistocardiogram, and the serum transaminase—will usually avert the making of such an error in a young individual

tion of the heart with functional mitral insufficiency, rupture of a congenital aneurysm of the membranous portion of the septum or of the sinus of Valsalva, rupture of one of the heart valves or of a chorda tendinea, and bacterial endocarditis with septal aneurysm formation.

Rupture of a Papillary Muscle. This complication occurs somewhat less frequently than does septal rupture. It exhibits a fairly characteristic course when sufficient observation is possible.[870d] A high pitched apical murmur is heard in about one half of the cases; it may be either systolic or diastolic. Interestingly, a thrill has not been observed—in marked contrast to the situation in septal rupture. On the other hand, a pseudofriction rub may be heard, this sign being attributed to the vibrations produced by the motions of the twisted chordae tendineae following the rupture. No unusual incidence of conduction defects is encountered here. Left-sided failure with acute intractable pulmonary edema and a rapid demise is the rule.

While 75 per cent of the septal perforations occur in the presence of anterior myocardial infarction, papillary muscle rupture is most often associated with posterior infarctions. In addition to the former complication, the differential diagnosis might include a ruptured mitral or aortic valve, a pre existing rheumatic mitral insufficiency, and ruptured chordae tendineae variously due to an endocarditis, a myocardial abscess,[870f] or spontaneous rupture.[870g]

Rupture of the Left Ventricle. Despite its dramatic appearance, serious implications, and relative frequency (being found in 9 per cent of fatal acute infarctions), this complication has attracted relatively little attention. This is particularly paradoxical at a time when new therapies are being introduced that might favor cardiorrhexis. The usual "clinical profile" consists of an acute myocardial infarction in a hypertensive patient with no antecedent old infarctions or congestive failure.[870h, 1] Rupture characteristically develops between the fourth and eleventh day after the infarction, at which time the necrotic tissue is most abundant.

The critical factor appears to be the presence of increased intraventricular pressure resulting from persisting hypertension, excessive effort (particularly in psychotic or mentally disturbed patients) and possibly the overaggressive use of levarterenol and other vasopressor agents. In all probability, there is little relationship to the use of either digitalis or anticoagulation therapy. (The incidence of myocardial rupture following myocardial infarction has run as high as 20 per cent in several large series of patients observed at institutions where anticoagulant therapy was not employed.) One case report is on record in which a loud systolic murmur and thrill occurred with rupture of the ventricle, simulating rupture of the interventricular septum.[870i]

Infarction of Either Atrium with or without Rupture. This complication has rarely been considered ante mortem. While atrial rupture is much less frequent than ventricular rupture, this diagnosis should be considered in the patient with evidence of atrial infarction or cardiac tamponade. An obliterative endarteritis of the atrial branches of the coronary arteries rather than a thrombotic occlusion is often found, with the right atrium rupturing three times more commonly than the left.[870k] In contrast to the

Rheumatic pancarditis and arteritis
Polyarteritis nodosa (p 307)
Thrombotic thrombocytopenic purpura (p 218)
Metastatic calcification (diseases of bone hyperparathyroidism, hypervitaminosis D chronic renal insufficiency) (p 25)
Thromboangiitis obliterans (p 216)
Friedreich s ataxia

6 *Increased cardiac load*
Anemia
Thyrotoxicosis (p 18)
Pheochromocytoma (p 21)
Pulmonary embolism (p 212)
Pulmonary hypertension (*hypercyanotic angina* ') (p 275)
Hypoglycemia
Rapid heart action
Obesity

7 *Myocardial insufficiency*
Also see under differential diagnosis of obscure heart failure and cardiomegaly
Endomyocardial fibroelastosis (p 232)
Chronic myocarditis (p 233)
Constrictive pericarditis (p 254)

COMPLICATIONS AND SEQUELAE OF MYOCARDIAL INFARCTION

Most internists are familiar with the more common complications of acute myocardial infarction, especially clinical heart failure venous thrombosis, arrhythmias of all types and embolization In view of the frequency with which the medical consultant is called in to see the coronary patient who is doing poorly, a brief (but necessarily incomplete) review of some other sequelae that are either commonly overlooked or infrequently considered will be set forth

Perforation of the Interventricular Septum This diagnosis can be readily made *if* there is sufficient time to observe the patient It is characterized by the appearance of a loud, low pitched, blowing systolic murmur at the left sternal border in the third fourth, or fifth interspaces, and is frequently accompanied by a thrill [870a, b] The murmur *is very distinct*, even though the heart sounds may be distant and the pulse feeble A pseudorub has rarely been encountered The presence of a diastolic murmur is unusual and can almost always be explained by the enlarged and dilated heart With the considerable fall in blood pressure that commonly takes place, there may be recurrence or intensification of the chest pain, refractory "right sided" congestive failure, or shock Significant electrocardiographic changes (most notably conduction defects) are observed in one third of these cases While 50 per cent will die within the first week, 13 per cent of patients with this complication have survived the second month, and individual cases much longer

These perforations of the ventricular septum might be overlooked by the pathologist because of the coarse trabeculations in the lower portion of the septum, and because small defects may be covered by thrombi Double rupture of the septum and of the free ventricular wall has been reported on rare occasions [870c] The differential diagnosis of the new murmur includes pericarditis with a friction rub the presence of a previous interventricular septal defect or aortic stenosis, rupture of a papillary muscle, acute dilata

after septal perforation In the latter case, the "rub' was replaced by the typical loud murmur within several hours Finally, pericarditis can occur in a dissecting aneurysm either as a complication of a coexisting myocardial infarction or subsequent to bleeding within the pericardial sac It must be appreciated that the latter need not be immediately fatal With a slow rate of oozing of blood into the pericardium surprisingly long periods of survival might be encountered [45] In such instances, there is almost always a concomitant fever and leukocytosis

Pleural Involvement Although the pleura is not commonly involved in uncomplicated myocardial infarction, a right sided or bilateral pleural effusion of variable size has been encountered This is especially true when myocardial failure complicates the infarction It is pointed out that the pleura can be actively involved in pulmonary embolism acute idiopathic pericarditis, and dissecting aneurysm (a distinct possibility when a large left hemothorax develops rapidly) [45]

An interesting postmyocardial infarction syndrome that is not infrequently observed consists of pleurisy pericarditis, and even a pneumonitis It closely simulates idiopathic pericarditis and the so-called postcommissurotomy syndrome In addition to the high incidence of both pericardial and pleural effusions and prolonged pericardial friction rubs there are apt to be protracted periods of low grade fever between the high peaks of fever severe pain of the pleuropericardial type, and a significant leukocytosis [871] There may be a paucity of objective findings however The frequent relapses in this condition along with the delay in its clinical onset (as long as ten weeks) explain why the diagnoses of pulmonary infarction or an extension of the original infarction are usually made by physicians who are not aware of this relatively benign entity Cortisone and its related steroids have proved effective in allaying the pain and fever in several instances

Pulmonary Involvement The presence of crepitant rales and platelike areas of atelectasis particularly on the left side, are very frequent findings in acute myocardial infarction [871f] Bibasilar or predominantly right sided rales may indicate the presence of congestive failure or pulmonary infarction Emphasis is again directed to unrecognized interstitial pulmonary edema presenting in the form of unexplained high fever within the first one or two weeks after the acute myocardial infarction [45] This fever usually proves resistant to antibiotic therapy but will promptly defervesce when diuretics are administered

Mediastinal Emphysema When it follows an acute myocardial infarction this complication is usually precipitated by concomitant left ventricular failure It can be readily misdiagnosed as heart failure *per se* prior to the appearance of the subcutaneous emphysema [871g] Extravasation of air into the perivascular sheaths and thence into the tissues of the mediastinum and the neck probably stems from the rupture of alveoli as a result of the cough dyspnea forceful straining, and other procedures leading to the Valsalva maneuver

In the presence of subcutaneous emphysema of the neck it is very important to consider the possibility of increased intramediastinal tension when marked dyspnea cyanosis, and dilated neck veins are also noted

situation in rupture of the ventricle, exertion is *not* a striking precipitating factor. Survival up to nine weeks has been observed.

The most rewarding clue to atrial infarction in the electrocardiogram is the finding of elevated or depressed PTa segments (particularly in leads II and III) and the sudden development of atrial arrhythmias.[870l] Unfortunately, the former changes are difficult to define in the absence of complete heart block. Two other rare sequelae of atrial infarction consist of aneurysmal dilatation of the atrial wall and mural thrombus formation, with or without ensuing embolic phenomena or obstruction.[870m]

Aneurysm of the Left Ventricle. This complication is found in approximately 9 per cent of patients who do not die shortly after the onset of their attack. It is usually noted on the anterior wall by fluoroscopy or x ray and is frequently asymptomatic. The finding of a dull first heart sound despite an increased area of cardiac dullness, a systolic murmur or gallop over an area of abnormal pulsation, and the persistence of a unique electrocardiographic pattern (elevated ST segments in all leads, right axis deviation in a heart that is enlarged to the left, and a high R wave in the right arm lead) are clues to its presence.[871a, b]

Fortunately, once the myocardial infarct has healed, there is little danger of rupture. Two other complications of aneurysm formation should be borne in mind, namely congestive heart failure and thromboembolic phenomena (due to the high incidence of mural thrombi). It is still debatable whether hypertension predisposes to or protects against this complication.

Pericardial Involvement. The considerable difficulties heretofore encountered by able cardiologists in the differentiation of atypical cases of acute idiopathic pericarditis and the pericarditis secondary to myocardial infarction are well known. Even though it represents a valuable diagnostic contribution, the clinical availability of the serum transaminase and related tests may be of little value under such circumstances in individual cases.

A pericardial reaction has been observed in approximately one out of five acute infarctions. Characteristically, it is attended by an ephemeral friction rub and an insignificant pericardial effusion. The persistence of the pericardial friction rub, or its initial appearance or recurrence after the first week suggests that either the diagnosis of myocardial infarction is in error or that certain complications may have taken place. Concerning the latter, particular note is made of hemopericardium, especially in the patient who shows a marked hypoprothrombinemic effect from dicoumarin or its analogs.[871c] The evacuation of this pericardial blood is attended by considerable improvement of any associated circulatory failure. It is apparent that the greater the tendency to cardiac dilatation and failure in the patient who has experienced an infarction the less will be the amount of pericardial fluid needed to create a tamponade effect, and the greater the difficulty in distinguishing it from simple myocardial failure.[871d]

Attention is drawn to several features in the differential diagnosis. A sound resembling a rub and heard over an area localized to the pulmonic valve may be encountered in pulmonary embolism.[45] A pseudo friction rub has also been heard following rupture of a papillary muscle or (rarely)

monary embolism are often clinically replaced by syncopal or anxiety attacks, angina pectoris, congestive failure paroxysmal auricular fibrillation, vague epigastric distress, hyponatremia, and the triad of tachycardia, digitalis toxicity, and mercurial fast edema (p 212)[777, 778]

Bean has called attention to the fact that hemiplegia can be the presenting manifestation of an acute myocardial infarction, but is not necessarily due to an embolus[871m] Both hemiplegia and various focal or general neurologic signs (confusion, coma convulsions delirium fainting) may result from the reduction in cardiac output and the subsequent cerebral anoxemia in the patient with concomitant cerebral arteriosclerosis

In a similar manner, the occlusion of a peripheral artery after a myocardial infarction can be due to local thrombus formation rather than to embolic obstruction Attention is directed to the possibility of venous or arterial thrombosis resulting from the sudden cessation of anticoagulant therapy and the presumed (but not conclusively proved) hypercoagulability state that ensues[1, 678] Phlebothrombosis, thromboembolism and cerebral thrombosis may also represent the occasional sequelae of rapid and vigorous diuresis, with the ensuing hemoconcentration and increased blood viscosity[772, 773]

Hiccups Little has been published concerning this complication of acute myocardial infarction, which is usually attended by an extremely poor prognosis While it might be due to a direct irritation of the diaphragmatic pleura in infarctions involving the posterior wall it probably primarily represents a reflex reaction from the superficial and deep cardiac plexuses *in most instances*[871n] *In patients with persistent singultus large* doses of quinidine or even a phrenic nerve crush may be required

Reflex Sympathetic Dystrophy and the Postcoronary Anterior Chest Wall Syndrome Reference was made in the preceding chapter to the shoulder hand syndrome and the resulting painful shoulder causalgia like stiffness, swelling and pain of the hand and fingers and the subsequent irreversible changes (atrophy of the hand muscles and subcutaneous tissues Dupuytren like contractures and osteoporosis) if neglected (p 221)[809] Periarthritis of one or both shoulders develops in about 15 per cent of patients within the first few weeks of the acute infarction While this process results primarily from the strong activation of the internuncial pool in the T1–T4 levels of the cord other factors often come into play namely the atrophy of disuse and the periarthritic personality

Early recognition of this syndrome is mandatory inasmuch as considerable mental anguish concerning continued coronary activity and unnecessary bed rest will be obviated Furthermore early local therapy with the steroids and nerve blocks may be curative Many patients have developed severe cardiac neuroses due to the presence of an undiagnosed reflex sympathetic dystrophy or to the development of the ' anterior chest wall syndrome The latter occurs with great frequency after a myocardial infarction generally lasts months or even years and might readily be confused with status anginosus[867d]

Complications of Therapy A number of potential hazards relating to therapeutic measures *per se* in the management of acute myocardial infarction have been ably reviewed by Russek[871] A brief résumé of this most

In this situation, a relatively small amount of such entrapped air might prove to be rapidly fatal if decompression procedures are not promptly instituted A lateral view of the chest is often helpful in demonstrating the presence of air behind the sternum

Abscess Formation in the Heart A suppurative infection within a recent bland myocardial infarct may result from a concomitant bacteremia, particularly in elderly and debilitated individuals In the several cases of this complication that have been recently reported, a pyogenic pneumonia due to a hemolytic *Staphylococcus aureus*[871h] or an acute pyelonephritis due to *Escherichia coli*[871i] were the associated septic lesions Cardiac rupture and hemopericardium have complicated such an abscess, but evidences of septic emboli in other organs are usually lacking The rarity of local abscess formation at the site of a myocardial infarction is actually rather difficult to explain

Another variation of intracardiac sepsis that can follow a coronary insult consists of an infection involving a mural thrombus in the left ventricle Rupture of the myocardium might even take place through such a lesion [871j] When a complicating endocarditis arises in the presence of mural thrombi following a myocardial infarction the diagnosis may be quite obscure if no murmur is heard [409]

Obstruction by an Intramural Thrombus The production of a functional aortic stenosis by a large mural thrombus in the left ventricle following a recent myocardial infarction was mentioned earlier in this chapter This diagnosis is particularly within the realm of antemortem achievement if the discovery of a new murmur consistent with that of aortic stenosis exhibits changes with position, being most prominent when the patient is recumbent [863e] There are also several instances on record of the syndrome of intermittent tricuspid valve occlusion due to a large occlusive postinfarctional thrombus involving the right atrium [870m]

Symmetric Peripheral Gangrene This complication infrequently follows the prolonged vascular collapse associated with acute myocardial infarction [871k, 1] In these cases not only are the femoral and pedal pulses readily palpated but carefully performed dissection of the arteries in the affected extremities usually fails to reveal any organic occlusion Although vasopressor drugs were administered to some of these patients this selective vasoconstriction has occurred either after the drug was discontinued or where such therapy was not even employed A similar type of nonocclusive gangrene has been reported in cardiac shock due to a number of underlying conditions (congestive failure mitral ball valve thrombus tight mitral stenosis, paroxysmal tachycardia), pulmonary infarction, and a number of infections (p 220)

Embolization and Hemiplegia The clinical syndromes associated with cerebral, renal, intestinal retinal and peripheral arterial embolism following acute myocardial infarction are well known and will not be further amplified at this point It has been suggested that the incidence is higher with continued activity in the presence of unrecognized infarction and particularly so when the process is complicated by a ventricular aneurysm [871a] In a previous chapter, great emphasis was placed upon the general experience that the classic pleurisy, dyspnea, and hemoptysis of pul

injection of Regitine into tissues rendered ischemic by the subcutaneous extravasation of levarterenol has prevented subsequent ulceration)

AMINOPHYLLINE May result in palpitations nausea, chest pain syncope, the "alert reaction" and sudden death if given too rapidly intravenously

PAPAVERINE May result in hypotension, collapse, and serious ventricular rhythms if given intravenously

ALCOHOL May result in tachycardias and ectopic arrhythmias

PULMONARY HYPERTENSION AND PULMONARY HEART DISEASE

A few comments are in order concerning the subject of pulmonary hypertension with particular reference to the concept of the primary" type Most observers agree that some anatomical abnormality or pathologic lesion can almost always be found—*if* carefully looked for—either in the heart the larger vessels or the smaller pulmonary arteries and veins Such conditions include multiple pulmonary arterial emboli or thrombi emphysema the granulomata inflammatory pulmonary diseases, diffuse interstitial fibrosis of the lungs the various forms of arteritis, nonfatal amniotic pulmonary embolism obstruction of the major pulmonary veins, sickle cell disease schistosomiasis lymphangitic carcinomatosis, constrictive pericarditis (when predominantly left sided), various types of congenital and acquired heart disease (mitral stenosis, atrial or ventricular septal defects chronic left ventricular failure from any cause) and deformities of the thorax

Edwards and Burchell have emphasized this concept when the diagnosis of '*Ayerza s disease*" (a term which they feel has no actual pathologic definition) is considered [872] Parmley and Jones and others have also critically reviewed the subject of *primary pulmonary arteriolosclerosis*, both in the previous literature and in their own case material [872b, 873] The process in the several patients meeting their pathologic criteria was of unknown cause All exhibited respiratory symptoms early in their clinical course which were subsequently followed by the rapidly progressive signs and symptoms of right heart failure Both clubbing and cyanosis are infrequent in primary pulmonary hypertension When the latter is encountered there is usually an associated patent foramen ovale

It is possible that in some instances of severe pulmonary hypertension the left coronary artery could be compressed for its proximal first centimeter as it passes between the aorta and the pulmonary artery within the pericardial sheath The Raynaud phenomenon has been observed in several patients with primary pulmonary hypertension the indirect inference being that there may be a concomitant spastic vasomotor process also affecting the pulmonary arterioles [87]

As in the case of aortic stenosis essential pulmonary hypertension can be a distinct cause of effort syncope [873] Such syncopal attacks are rare in congenital heart disease with pulmonary hypertension, apparently due to the usual adequacy of the associated right to-left shunt in preventing cardiac and cerebral ischemia This disorder is also stressed because of the fact that the lives of these patients are under continual menace For

important subject will be set forth, based upon a modification of this author's outline

NITROGLYCERIN May paradoxically precipitate or aggravate coronary insufficiency and shock in certain individuals, particularly when given in doses of 1/100 grain, may excite dangerous ectopic tachycardias (as a result of reflex stimulation of the cardiac accelerators)

MORPHINE May increase susceptibility to ventricular ectopic rhythms, may produce abdominal distention, urinary retention, respiratory depression, and vomiting with retching, increases biliary pressure also exerts antidiuretic and hypotensive effects, particularly when the erect position is assumed, opiates may in themselves induce increases in the activity of the serum transaminase—in large measure due to the acute spasm of the duodenum and of the biliary tract which is so induced[8694]

OXYGEN May induce apprehension and claustrophobia, local irritation is often produced by nasal catheter and mask, differences in potential in the arteriosclerotic heart can be induced that may increase the tendency to ventricular fibrillation

ANTICOAGULANTS Hemorrhagic complications (gastrointestinal, pericardial, nervous system renal retroperitoneal) and even death might occur, may provide a false sense of security concerning both extension of the coronary occlusion and thromboembolic phenomena, "rebound" hypercoagulability and thrombosis may take place if dicoumarin is suddenly discontinued

HOSPITALIZATION The attendant physical and psychic influences associated with the patient's removal may incite or potentiate ventricular fibrillation, shock, or unnecessary anxiety during the vulnerable first two days

BED REST May contribute to thromboembolism, constipation, anxiety, loss of muscular or vascular tone, atelectasis, hypostatic pneumonia, and osteoporosis

"CHAIR TREATMENT" The physical activity may lead to ventricular fibrillation or standstill and cardiac rupture as this program is currently practiced in most quarters it may augment the hypotensive effect of opiates, the patient often experiences a false sense of well being

DIGITALIS Intoxication may be induced more readily in the presence of an acute infarction digitalis may incite various ventricular and auricular arrhythmias due to both its local and vagal effects

QUINIDINE Various side effects can occur (nausea, vomiting diarrhea), cardiac arrest or ventricular tachycardias have resulted particularly when administered in the presence of prolonged intraventricular conduction or heart block, quinidine is known to be able to produce such idiosyncrasies as a drug fever, petechiae purpura,[8710] and even splenomegaly[403b]

PRONESTYL May cause marked hypotension particularly when given via the intravenous route, cardiac arrest or ventricular fibrillation can be induced, the former being most apt to take place in the presence of prolonged intraventricular conduction or heart block

PRESSOR AGENTS May result in dangerous elevations of the blood pressure, may aggravate congestive heart failure possibly may contribute to cardiac rupture, local gangrene can be due to Levophed (The prompt

heart disease aneurysm or idiopathic dilatation of the pulmonary artery, kyphoscoliosis, and the patient s age and habitus [876b] The various causes of enlargement of the pulmonary artery are also considered later in this chapter under the discussion of malformations of the heart (p 280)

Pulmonary heart disease may be due to many of the conditions cited as causes of pulmonary hypertension and deserves the same careful cor relation of the clinical radiographic, and cardiac pulmonary function findings The term "cor pulmonale covers a number of unrelated condi tions that have little in common beyond the fact that there is failure of the right ventricle [876] It is quite likely that much of the increase in the incidence of cor pulmonale in the years to come will reflect the greater control of previously fatal bronchopulmonary infections and suppuration, both of a tuberculous and nontuberculous causation, leaving the residues of fibrosis emphysema, and vanishing lungs [876d]

When the cause and site of obstruction in a case of cor pulmonale are in doubt (that is, embolic obstruction of the pulmonary arteries versus obstruction on the venous side or in the left atrium or mitral valve) the demonstration of clear lung fields is often helpful in pointing to the former

Exhaustive studies on the cardiopulmonary function of patients with pulmonary tuberculosis at the Bellevue Hospital and elsewhere have pointed out that the uncomplicated form of this disease (that is without emphysema, collapse therapy or surgery) has little influence on either the cardiac output or the pulmonary artery tension at rest and after exercise [127 1] This information tends to refute the long standing belief that pulmonary tuberculosis *per se* is a common cause for cor pulmonale or pulmonary emphysema

The severe pulmonary arteriolar sclerosis that can develop in response to long standing pulmonary hypertension of a high order is now no longer regarded as academic in view of the continuing progress in the correction of congenital heart disease This is of particular importance in the case of interventricular septal defects wherein the therapeutic paradox of acute postoperative right heart failure is apt to ensue when such changes are present [879] This might be anticipated if the pulmonary pressures are found to approach or to exceed 80 per cent that of the systemic blood pressure preoperatively The electrocardiogram may be helpful in differentiating a ventricular septal defect from a single ventricle since evidence of a thick right ventricle is not present in the latter situation

The importance of recognizing the development of pulmonary hyper *tension in patients with long standing patent ductus* arteriosus and the subsequent effects stemming from a reversal of the flow of blood from the pulmonary artery to the aorta will be discussed later in this chapter (p 285)

The relationship of *pectus excavatum* (funnel chest trichterbrust) to significant derangements in cardiopulmonary physiology continues to be overlooked or minimized by many physicians The disability results from a number of factors including a decreased return of blood to the right heart, cardiac arrhythmias secondary to atrial impingement restriction of the heart s expansion and a decrease in the respiratory reserve [876e] This is very definitely a form of heart disease that is potentially curable by a subperichondral resection of the deformed costal cartilages

example, death has followed the performance of various otherwise benign procedures, including barbiturate anesthesia determination of the circulation time and more frequently cardiac catheterization[874]

The clinician must be aware of one very important and potentially therapeutic consideration prior to making the diagnosis of primary pulmonary hypertension In the experience of men such as Dexter, recurrent and extensive pulmonary embolism will be found in one half of these individuals at postmortem examination This is true even when all the diagnostic criteria for the primary disease appeared to be present, and there was no hint that either embolism or thrombophlebitis had ever been present[877a, 876]

Thrombosis of the major pulmonary arteries is suggested by the presence of progressive right ventricular heart failure associated with new or changing heart murmurs syncopal attacks, dry lungs (despite concomitant dyspnea ascites, and peripheral edema), and a poor response to therapy If there is an awareness of this possibility in the patient who is already a candidate for thromboembolic disease the diagnosis might be made on chest films by the demonstration of blunting or deformity of one or both pulmonary arteries along with an associated diminution in the affected pulmonary vascular markings[875a] Since there is not always a cut off of the pulmonary artery when a thrombosis of the pulmonary artery is present, one may have to rely on the fluoroscopist's impression that there is an intrinsic pulsation of this vessel in ruling out the possibility of pulmonary embolism

Stenosis of a main branch of the pulmonary artery ('coarctation of the pulmonary artery) bears significance not only as it relates to the development of pulmonary hypertension but also because a continuous ductus-like murmur may be heard before the hypertension develops On the basis of this murmur a thoracotomy may be performed in search of a patent ductus arteriosus[875b] The bruit can be explained by the presence of the proximal arterial bed which acts as a reservoir under pressure Within a relatively short space of time 24 cases of stenosis of the pulmonary branches have been diagnosed by five groups of investigators

Williams Lange and Hecht have pointed out a number of diagnostic pitfalls and surgical considerations that may have an important bearing in suspected instances of such postvalvular constriction of the pulmonary artery[875c] These include the following (1) one must be sure that an inadvertent wedging of the cardiac catheter is not producing a spurious pressure rise (2) recordings taken near a patent ductus arteriosus may show a higher pressure than that recorded distally (3) severe pulmonary stenosis may mask the presence of an associated but more distal pulmonary arterial constriction and (4) marked postvalvular constriction can closely mimic pulmonary stenosis

When confronted with an *enlargement of the pulmonary conus pulmonary artery segment area* and a marked accentuation of the second pulmonic sound in the absence of mitral stenosis it is wise to consider several additional causes These include congenital heart disease (interatrial septal defect Lutembacher s syndrome high interventricular septal defect, patent ductus arteriosus, Eisenmenger s complex pulmonic stenosis) thyroid

portant variations and complications which could be of diagnostic and therapeutic significance to the consultant physician or to the cardiologist who does not confine his efforts to pediatric disorders Such entities include postvalvular pulmonary artery stenosis (p 276), the sequelae of pulmonary hypertension resulting from interventricular septal defects (p 277) and the vulnerability of bicuspid aortic valves to bacterial infection or to supravalvular aneurysm formation (p 116) Inasmuch as patent ductus arteriosus and the tetralogy of Fallot represent two of the more frequent congenital anomalies however some of the important and not too uncommon deviations from their classical pictures will be elaborated upon below

Three of the chief reasons for presenting a section on congenital malformations of the heart are to indicate that they are by no means confined to infants and children (to wit, the frequency with which interatrial septal defects are encountered in adults), that they may simulate acquired diseases of the heart (for example, Ebstein s anomaly suggesting rheumatic tricuspid and mitral valvular disease) and that accurate diagnosis is especially necessary in light of the number of techniques now available in large centers for the open repair of many malformations and the progressively declining mortality rate of these procedures

The extended knowledge on the subject of congenital heart disease which has been derived in recent years underscores the fact that one may be in serious error if the diagnosis is made too casually on the basis of a history and physical examination alone For example, while it is true that the association of a right bundle-branch block and marked dilatation of the primary branches of the pulmonary artery are highly suggestive of an atrial septal defect in patients with a prominent systolic murmur over the base of the heart there have been so many instances where such was not the case that accurate diagnosis can be achieved only by cardiac catheterization The reader is referred to the guide for the evaluation and management of congenital cardiac defects which has been set forth by the Committee on Congenital Heart Disease of the American Heart Association It is of particular value with reference to the proper timing of diagnostic studies and surgical correction [877]

The recent report by Gasul and Fell of a comprehensive nine year study of 1395 patients with congenital heart disease—90 per cent of whom were under the age of sixteen years—gives one a useful frame of reference as to the actual incidence of the various entities in practice [877b] The table on page 280 summarizes the experiences of these authors as set forth in their report (a number of the rarest anomalies are purposely omitted) References have been added to this list including several unusual entities whose rarity precludes further discussion in this text

A number of considerations relating to the physical signs (viz cardiac hypertrophy cyanosis, murmurs, heart sounds) and the differential diagnosis of congenital heart disease were discussed earlier in this chapter (pp 232–233 and pp 237–243) Several radiographic aberrations due to various congenital cardiac or large vessel anomalies which may be confused with mediastinal tumors are considered in a later chapter (p 342)

The prominence of both the pulmonary artery segment and the hilar markings are obviously of considerable value in any analysis of congenital

Scurvy, rickets, and obstructive lesions in the respiratory tract actually play only a small part in the cause of this deformity It is well to bear in mind both the increased familial incidence and the association of this condition with Marfan's syndrome[1254, 1255] If the funnel chest is unrecognized in a single posteroanterior chest film, the loud murmur, the shift of the cardiac silhouette to the left, and the electrocardiographic findings (primarily due to cardiac rotation and not to myocardial damage) are very apt to be regarded as evidences of either rheumatic or congenital heart disease[876e]

The significant cardiac strain in patients with *extensive pulmonary disease* might not even be suspected prior to the onset of increasing dyspnea, distended neck veins, edema, and hepatomegaly unless a circulation time, an electrocardiogram, and careful x ray studies are done The pathogenesis of this form of heart failure (most notably as it also affects the left ventricle) has been better comprehended in recent years The demonstration of the extensive anastomoses between the enlarged bronchial arteries and the pulmonary arteries, along with the added complicated interplay of the arterial desaturation, "secondary" polycythemia, pulmonary hypertension, and impaired pulmonary function are all significant factors[879] There has been a tendency to overlook the effects of chronic pulmonary disease on the renal circulation Exacerbations of the lung disease may initiate renal ischemia, which could in turn precede the development of pulmonary heart failure[876f]

The recognition of pulmonocardiac failure due to kyphoscoliosis and other deformities of the chest cage merits added emphasis because of the great sensitivity of these patients to the narcotics[880a] Similarly, if simultaneous therapy directed to the respiratory disease is not instituted—particularly in patients with marked oxygen unsaturation and carbon dioxide retention—digitalization may incur marked toxicity and further deterioration of pulmonary function[880b] The interesting neurologic syndrome associated with chronic pulmonary insufficiency and at times confused with a brain tumor will be considered in a later chapter (p 366)

The settling of approximately one million immigrants from Puerto Rico in the United States justifies some interest in *schistosomal cor pulmonale* The pathological basis for the pulmonary hypertension in *Schistosoma mansoni* infection is probably the widespread obliterative arteriolitis that stems from the repeated embolization of ova into the pulmonary arterioles (which are simultaneously in a hypersensitivity state)[6 6 6 7b] This entity should be considered, along with rheumatic and congenital heart disease, in a young patient from an endemic area who exhibits dyspnea, hepatosplenomegaly, an accentuated pulmonic second heart sound, cardiac murmurs, and other evidences of right sided failure

GENERAL CONSIDERATIONS PERTAINING TO THE DIAGNOSIS OF CONGENITAL HEART DISEASE

No attempt will be made to set forth elaborate discussions of the divers congenital cardiac anomalies or their differential diagnoses in this text Most of the comments on congenital heart lesions are limited to those in

circulation, any attempts at classification of this finding should be related to the presence or absence of primary changes in the pulmonary hemodynamics Liu and Lima have set forth such an approach to this problem in the following listing [876b]

PRESENCE OF PRIMARY CHANGES IN PULMONARY HEMODYNAMICS

I Increased pulmonary flow as the principal factor

A No increase in systemic flow Mostly in noncyanotic malformations with a left to right shunt the size of the pulmonary artery corresponds to the degree of pulmonary blood flow in addition to the increased pulsations of the main pulmonary artery, there may be a "hilar dance"

1 Atrial septal defect Lutembacher's syndrome, or anomalous pulmonary venous return
2 Ventricular septal defect
3 Patent ductus arteriosus or aortopulmonary defect
4 Atrioventricularis communis
5 Rupture of sinus of Valsalva into the right heart or pulmonary artery

B Increase in both the pulmonary and systemic blood flows The pulmonary artery enlargement may not be as striking inasmuch as the aorta and the left side of the heart share in the strain a "hilar dance" is rarely encountered

1 Peripheral arteriovenous fistula
2 Hyperthyroidism
3 Anemia
4 Beriberi heart
5 Pregnancy

II Increased flow in the pulmonary artery and its main branches (pulmonary insufficiency)

III Increased pulmonary arterial pressure as the principal factor

A Increased pulmonary arteriolar resistance

1 Without congenital lesion of the heart
   a Chronic cor pulmonale
   b Periarteritis nodosa
   c Multiple pulmonary embolism
   d Primary pulmonary hypertension
   e Syphilitic pulmonary endarteritis obliterans ("Ayerza's disease")
2 With congenital lesion of the heart
   a Atrial septal defect Lutembacher's syndrome or anomalous pulmonary venous return
   b Ventricular septal defect (Eisenmenger syndrome)
   c Patent ductus arteriosus with pulmonary hypertension
   d Taussig Bing syndrome

INCIDENCE OF TYPES OF CONGENITAL HEART DISEASE

	No of Patients	Per Cent
Ventricular septal defects[878m]	287	20.5
Tetralogy of Fallot[893]	156	11.1
Patent ductus arteriosus[881]	150	10.7
Atrial septal defects[878]	135	9.6
Undiagnosed (chiefly either atrial or ventricular septal defects)	112	8.1
Coarctation of the aorta (preductal and postductal)	78	5.5
Complete transposition of the great vessels	60	4.3
Pulmonary stenosis with atrial and/or ventricular septal defects[878g, h]	42	3.0
Isolated pulmonary stenosis[878e, c]	41	2.9
Common atrioventricular valves (all forms)	33	2.3
Aortic and subaortic stenosis[878b]	29	2.1
Eisenmenger complex[878i]	25	1.8
Tricuspid atresia[878]	24	1.7
Persistent truncus arteriosus[878o]	24	1.7
Dextrocardia with and without situs inversus	24	1.7
Primary endocardial fibroelastosis[835]	22	1.5
Idiopathic dilatation of pulmonary artery[878b]	18	1.2
Mitral atresia	13	0.9
Single ventricle	12	0.86
Tricuspid stenosis	12	0.86
Vascular rings	12	0.86
Mitral stenosis with and without fibroelastosis[878k]	10	0.7
Pentalogy (tetralogy of Fallot with atrial communication)	8	0.57
Ebstein's anomaly (the downward displacement of the tricuspid valve into the right ventricle)[878]	7	0.5
Levocardia (a left-sided heart in the presence of situs inversus of the viscera)[878j]	7	0.5
Taussig Bing heart (a transposed aorta combined with an overriding pulmonary artery)[878d]	7	0.5
Tumor of the heart[854]	7	0.5
Anomalous drainage of all the pulmonary veins[878e]	6	0.43
Anomalous left coronary artery[878f]	6	0.43
Primary pulmonary hypertension[873, 874]	6	0.43
Transposition of great vessels with pulmonary or aortic stenosis	4	0.28
Aortic septal defect	3	0.21
Ruptured sinus of Valsalva[901]	3	0.21
Arteriovenous pulmonary aneurysm[812]	3	0.21
Glycogen storage disease[829]	2	0.14
Lutembacher syndrome	1	0.07

heart disease that is characterized by right ventricular hypertrophy The pulmonary artery segment is prominent in the presence of interatrial septal defects, the Eisenmenger syndrome, a patent ductus arteriosus, and the poststenotic dilatation of pulmonic stenosis whereas it is usually not observed in the tetralogy of Fallot or transposition of the great vessels Since *enlargement of the pulmonary artery* (seen roentgenographically) holds an important role in the proper evaluation of congenital heart disease and since this enlargement is often associated with an abnormal *pulmonary*

with large pulmonary arteries single ventricle with large pulmonary arteries, and other malformations) [877b]

Considerations in the Diagnosis of Several Congenital Cardiac Malformations

A few abbreviated comments pertaining to several congenital cardiac malformations which may be of general interest to internists follow

1 The presence of central cyanosis clubbing of the fingers a precordial systolic murmur and evidence of left ventricular hypertrophy clinically and by electrocardiogram in a young child is highly suggestive of *tricuspid atresia* [878a]

2 One should not overlook the fact that a *pulmonic stenosis* can coexist with an atrial or ventricular septal defect In such a situation, the prominent pulmonary vascular markings and the presence of a loud pulmonic second sound could be misleading [877d] The typical murmur and the finding of right ventricular hypertrophy by electrocardiogram (in contrast to the expected normal pattern or an incomplete right bundle-branch block with uncomplicated septal defects) may give one a clue in this direction A relatively common cause for cyanotic congenital heart disease in infants for which a valvular operation (but not the Blalock or Potts procedures) may be very helpful is congenital pulmonic stenosis with an open foramen ovale [878b]

Within an eight year period 15 patients more than thirty four years of age were encountered at the Mayo Clinic who were conclusively shown to have congenital valvular pulmonic stenosis (without a ventricular septal defect) [878q] The degree of poststenotic dilatation of the pulmonary artery in such patients may initially bring them to medical attention for the evaluation of a left hilar mass

3 In a manner similar to that by which a relative stenosis of the aortic and mitral valves can result from a dilatation of the cardiac chamber just proximal to it there may also be a *relative pulmonic stenosis* when the *right ventricle is dilated in the absence of a concomitant distention of the* pulmonary valvular ring This has been demonstrated in some patients with mitral stenosis [877f]

4 The possibility of an actual *pulmonary atresia* should be entertained when a cyanotic infant presents without a significant heart murmur

5 *Coarctation of the aorta* is complicated in up to 40 per cent of the cases by a bicuspid aortic valve This additional malformation is by no means insignificant inasmuch as it may become the seat of a bacterial endocarditis or a rheumatic endocarditis [4 0d] The correct taking of the blood pressure in an infant suspected of having a coarctation of the aorta is obviously crucial Should the auscultatory method prove to be unsatisfactory, it can be reliably obtained by the u e of the flush technique with two cuffs [877e] Another reliable method for obtaining the blood pressure of the lower extremities consists in placing a cuff around the ankle and feeling for the systolic pedal pulse Weiss found that the foot systolic pressure determined in this fashion is usually within 15 mm of mercury of the

B Increased left atrial pressure
1 Without increased pulmonary arteriolar resistance
a Chronic left ventricular failure
b Constrictive pericarditis of the left ventricle
2 With or without increased pulmonary arteriolar resistance (mitral stenosis, mitral insufficiency, or both)

IV Increased systolic pressure gradient between right ventricle and pulmonary artery (pulmonic stenosis with poststenotic dilatation)

V Mixed types

A Increased pulmonary flow and increased pulmonary arterial pressure with or without pulmonic insufficiency listed in I, A, III, A, 1 a, and III, A, 2

B Increased pulmonary flow and increased systolic pressure gradient between right ventricle and pulmonary artery (pulmonic stenosis plus atrial or ventricular septal defect)

ABSENCE OF PRIMARY CHANGES IN PULMONARY HEMODYNAMICS

I Abnormal development or weakness of the pulmonary artery (or idiopathic dilatation of the pulmonary artery (The pulmonary artery shows a considerable increase in its width, but no increase in its pulsations or that of the hilar or peripheral pulmonary vessls, vague precordial distress may be present, *this diagnosis must be made* with caution in light of the readiness with which the following entities may be overlooked mild pulmonic stenosis, a small arteriovenous shunt, pulmonic insufficiency, or excessive exertion during adolescence)

II Acquired weakness of the pulmonary artery

A Rheumatic heart disease

B Mycotic infection of the pulmonary artery (subacute bacterial endocarditis)

C Syphilitic pulmonary arteritis

D Traumatic aneurysm

The subject of pulmonary artery enlargement was previously considered in this chapter under the discussion of pulmonary heart disease (p 276)

Gasul and Fell also make the following two pertinent observations concerning the feasibility of surgery in cyanotic patients with congenital malformations of the heart (1) if the evidence points to a heart that is not greatly enlarged and a definite reduction in the pulmonary vasculature, surgical correction of the defect (usually the tetralogy, tricuspid atresia, single ventricle with a pulmonic stenosis dextrocardia or levocardia with pulmonic stenosis) is probably feasible, (2) on the other hand, the presence of marked cardiac enlargement in association with a definite increase in the pulmonary vascular pulsations and markings probably indicates that a pathologic condition exists which is not correctible by surgery at the present time (namely, complete transposition of the great vessels, the Taussig Bing heart, the Eisenmenger complex, persistent common trunk

cardial fibroelastosis or marked subaortic stenosis[877, 878f] Other causes of cardiomegaly in young children who do not have murmurs or abnormal blood pressures are viral and idiopathic myocarditis[836c] glycogen storage disease of the heart[8 9c] and medial necrosis of the coronary arteries[836b]

Furthermore there are times when one can diagnose auricular enlargement (namely by large and peaked P_2 waves in the case of the right atrium, and by broad P_2 waves when the left auricle is enlarged) Considerable enlargement of the right auricle and a high degree of pulmonary congestion in an infant who has survived for several months suggests that there is drainage of all the pulmonary veins into the right auricle[878e]

An enlarged thymus gland could cover most of the cardiac silhouette and simulate cardiac enlargement In such a situation the effects of respiration on the chest films and the palpation of the apical impulse in the normal area can be quite helpful

11 *Ebstein s anomaly* is mentioned primarily to point out that in addition to the cyanotic form of the disease occurring in children, the malformation may be found in adults in the form of a noncyanotic cardiomegaly accompanied by a fairly good exercise tolerance Furthermore, the nature of the valvular abnormality could mislead the clinician into making the diagnosis of rheumatic tricuspid valvular disease (or conceivably of carcinoid heart disease) and rheumatic mitral valvulitis[878c] (The auscultation of an accentuated first heart sound and of an opening snap at the apex has been attributed to the displacement of the tricuspid valve to the left)

Several possible clues to the presence of this unusual but interesting disorder include the following (1) the finding of cyanosis in the absence of hypertrophy of the right ventricles (2) the demonstration of a complete right bundle-branch block with low amplitude R waves in the right precordial leads (presumably due to the thinning and dilatation of the proximal portion of the right ventricle which has become "atrialized'), (3) evidence of hypertrophy of the right atrium by the tall broadened P waves in the limb leads and over the right atrium and by x rays, (4) the tendency to supraventricular arrhythmias and (5) the characteristic hemodynamic pattern on cardiac catheterization (viz evidences of a markedly enlarged right atrium normal pressures in the pulmonary artery and right ventricle and the absence of an arteriovenous shunt)

12 Since *maternal rubella* usually occurs during the spring months the birthdays in November or December of children who have congenital cardiac defects might be retrospectively significant in this regard

COMPLICATIONS AND VARIATIONS OF PATENT DUCTUS ARTERIOSUS AND THE TETRALOGY OF FALLOT

The various causes for continuous murmurs and hums which might be mistaken for a *patent ductus arteriosus* were considered earlier in this chapter (p 242) While only the systolic component of the murmur of a patent ductus arteriosus may be audible it can be recognized more accurately in infants by noting the late systolic accentuation and its prominence over

brachial blood pressure[877e] A coarctation might be suspected when it is at least 10 mm of mercury lower than that of the arm

6 The author is familiar with one instance in which an astute diagnosis of *dextrocardia* was made by a urologist who noted the presence of a right-sided varicocele (due to an associated situs inversus) which could not be explained by a tumor or other local pathologic condition

7 There is usually little difficulty in diagnosing *congenital aortic stenosis in early childhood* (*Rheumatic valvulitis is unusual in children below the age of four years*) Here again, surgery should not be deferred too long in the presence of a physiologically significant lesion due to the possibilities of rapid decompensation or sudden death In reviewing an experience with 37 of these patients, Downing encountered an associated coarctation of the aorta in 8 and pulmonary stenosis in 4[878b] The presence of an aortic second sound may be of value in distinguishing between an aortic valvular stenosis and a subaortic stenosis

8 *Congenital mitral stenosis* is usually associated with aortic stenosis, coarctation of the aorta, or a patent ductus arteriosus, rather than occurring as an isolated malformation[878k] While it is very infrequent, its significance lies both in the early mortality and in the fact that its presence precludes successful surgical correction of the associated lesions The diagnosis is admittedly quite difficult, although it may be suspected when right sided hypertrophy is encountered in the presence of a recognized left sided lesion

9 Both the rarity of the *Lutembacher syndrome* and the relative frequency with which patients with congenital defects that involve the auricles develop rheumatic lesions should be considered before this *diagnosis* is made The finding of a mid diastolic rumble in the enlarged heart with an atrial septal defect is indicative of a relative tricuspid stenosis and the high flow across this valve rather than a true associated mitral stenosis (the Lutembacher syndrome)[877b] Since the clinical and laboratory findings may be identical in patients with the Lutembacher syndrome and with atrial septal defects in whom there are elevated atrial pressures *due to left* ventricular failure, the differentiation can be made only by demonstrating the diastolic pressure gradient between the left atrium and the left ventricle

10 Inasmuch as only a few disorders cause enlargement of the fetal heart the presence of *cardiac enlargement shortly after birth* may be of considerable importance In view of the diagnostic limitations of x ray in infancy in this regard, the voltage of the complexes in the precordial leads is considered to be the most reliable indicator of chamber enlargement when dealing with this age group (One must recognize the normal preponderance of the right ventricle, however) Congestive failure in infancy is frequently mistaken for pneumonia One must be cautious in ascribing too much significance to the finding of a palpable liver several centimeters below the right costal margin in infants with congenital heart disease inasmuch as this is often a normal feature in this age group

The marked left ventricular hypertrophy pattern that is produced by an anomalous origin of the left coronary artery from the pulmonary artery cannot be distinguished electrocardiographically from that of either endo-

instead of the term '*tetralogy of Fallot*,' such functionally descriptive designations as "ventricular septal defect with mild pulmonary stenosis and left to right shunt," "ventricular septal defect with moderate pulmonary stenosis and bidirectional shunts," or "ventricular septal defect with severe pulmonary stenosis and right to left shunt" be employed [879c] The assumption of the squatting position by cyanotic children when they are tired is usually indicative of pulmonic stenosis and decreased pulmonary flow as occurs most strikingly in this disorder

In line with this terminology, others have clearly demonstrated that only two features of the "tetralogy" are actually essential—viz, the pulmonary stenosis and the ventricular septal defect [893f] The right ventricular hypertrophy is essentially a secondary phenomenon, while the dextroposition of the aortic root has very little bearing upon the hemodynamic pattern present The latter observation is supported by the fact that there is usually no technical difficulty encountered relative to the position of the aorta when the ventricular septal defect in the tetralogy of Fallot is closed

Attention is directed to the review by Holladay and Witham of the variations which can be produced by the tetralogy of Fallot [893a] Cyanosis need not necessarily be present at birth In fact it may not become apparent until the child begins to crawl or to walk Furthermore, because of the relatively unstable nature of the hypoxia, there is no clear cut relationship between the hemoglobin level and the degree of oxygen saturation The fall in oxygen consumption after exercise which occurs in pulmonic stenosis helps to differentiate patients having the tetralogy from those with the Eisenmenger complex (in which no pulmonic stenosis exists)

Some of these patients (perhaps 10 per cent) may reach their second decade In such instances there is usually a predominant valvular pulmonic stenosis rather than a stenosis of the infundibular type The pulmonic second sound is frequently prominent in contrast to the case with an isolated pulmonic stenosis Within the clinical spectrum of patients with the tetralogy of Fallot is the acyanotic patient who is active and who is usually regarded as having a large ventricular septal defect [893t] In addition to the large defect however there is a very mild infundibular stenosis, resulting in a large left to right shunt without a right to left shunt There are instances wherein acute and chronic rheumatic endocarditis have complicated the tetralogy of Fallot [893] Mention was made in an earlier chapter of the possibility of a brain abscess complicating cyanotic heart disease in which a right to left shunt exists (p 133)

In addition to the evidences of right ventricular hypertrophy both in the physical examination and in the electrocardiogram one should be aware of the fact that these patients may also develop hypertension, left ventricular hypertrophy marked cardiac enlargement, and congestive failure Accordingly an increased cardiothoracic ratio does not necessarily imply additional complicating anomalies but may merely reflect a severe infundibular stenosis or hypertension (a poor prognostic sign) Furthermore it has been stressed that the classic "coeur en sabot" is demonstrable only in the minority of infants with this condition [893]

The considerable dilatation of the bronchial arteries that frequently evolves in the tetralogy may give rise to much diagnostic confusion First,

the back. Even the presence of minimal cyanosis in the patient with a patent ductus arteriosus should immediately suggest some complication.

One must pay close attention to the finding of sharply peaked P_1 waves and evidences for hypertrophy of the right ventricle in the patient with a patent ductus arteriosus. These findings could be indicative of a concomitant pulmonary stenosis. This last mentioned defect must be corrected by the surgeon *before* that of the ductus in order to prevent the precipitation of the patient into acute right-sided heart failure.

Marked pulmonary hypertension may develop in the patient with a long standing patent ductus arteriosus. This phenomenon is usually associated with a *reversal of the flow of blood from the pulmonary artery to the aorta* as a result of the development of increased pulmonary resistance.[881] It is not unlikely that in most instances of pulmonary hypertension which complicate a patent ductus arteriosus the pulmonary hypertension was initiated very early during infancy.

The recognition of this situation is important for several reasons. First, the character of the clinical picture often changes. This is particularly true with regard to the murmur (which may either lose its systolic or diastolic component, or even disappear entirely). Secondly, the finding of cyanosis, a systolic murmur, and evidence of right ventricular strain may lead to an erroneous diagnosis of pulmonic stenosis. Thirdly, patients may survive for many years after the onset of the reversed flow.[881a] Finally, sudden death has followed ligation of the ductus arteriosus and various physiologic stresses (such as childbirth) in the presence of this complication.[881c]

The diagnosis of a reversed flow can be suspected when there develops evidence of right ventricular hypertrophy in both the electrocardiogram and chest films in the patient with a patent ductus, and when cyanosis makes its appearance. The cyanosis is usually most pronounced in the lower extremities (since the deoxygenated blood enters the aorta distal to the carotid and subclavian arteries). The diagnosis is conclusively established by cardiac catheterization and by the demonstration of a higher arterial oxygen saturation in the right arm than in the femoral artery on simultaneously drawn specimens of blood.

In the light of both the hazardous nature of any attempts to close the ductus if a predominant right to left shunt exists, and the obvious hazard of subjecting these patients to thoracotomy in order to observe the effects on the pulmonary artery and systemic pressures following occlusion of the ductus, preoperative evaluation might be attempted should a reversed flow be suspected. This is performed by occluding the ductus during cardiac catheterization (if possible) by means of a special three-way catheter with an inflatable balloon which is placed into the patent ductus. Such a technique permits the accurate calculation of both the pulmonary artery pressures and the magnitude of the shunts in the presence of a bidirectional flow.[881d] A marked rise of the pulmonary artery pressure after a four minute occlusion indicates the presence of a major right to left shunt for which the patent ductus is serving as an escape valve.

Inasmuch as the functional derangement of the same anatomic defect may vary considerably in individual cases, Edwards has suggested that

cardial friction rubs with changes in position the intensification of a gallop rhythm in the recumbent position the detection of pulsus alternans in the upright position the greater sensitivity of the carotid sinus reflex in the sitting position especially in the digitalized patient the greater ease of detecting the murmur of aortic insufficiency with the patient sitting and bending forward and the relief of the orthostatic dyspnea of emphysema and interstitial pulmonary fibrosis by the recumbent position The accentuation of cardiac dyspnea, angina pectoris and heart failure by recumbency can be better appreciated in light of the fact that there is a release of 500 ml of blood or more from the lower limbs back into the circulation during the change from the upright to the flat position, even in normal individuals

It must be stressed that the finding of 'low blood pressure in the vast majority of individuals in whom it is encountered is merely a coincidental physical finding Only rarely does it represent the primary cause of the patient s dizziness asthenia poor concentration, sweating and head ache All too often, essential hypotension" is a vicious iatrogenic affliction In fact the author is continually impressed with the fact that many of these patients have unusually good health and vigor particularly after the age of fifty (The reason that individuals with relatively low systolic pressure readings experience no untoward effects is that the greatest fall in blood pressure actually occurs in the passage of blood from the arterioles to the capillaries where the circulation can function effectively under a pressure of approximately 20 mm of mercury)

There are many variants of the syndrome of *chronic postural hypotension* The postural syncope is most apt to be worse shortly after rising in the morning However, this disorder is more frequently a manifestation of some disease or therapeutic effort (hypotensive drugs sympathectomy, adrenalectomy) that affects the autonomic nervous system It must also be differentiated from myocardial infarction constrictive pericarditis chronic infections, anemia malnutrition Addison s disease, primary autonomic insufficiency [1139] and dysautonomia [1140] The last two entities are discussed elsewhere (p 381)

Orthostatic hypotension may be a striking feature in elderly individ uals who have lost much weight over a relatively short period of time and who lead very sedentary lives The great therapeutic benefit of an abdom inal binder a tight belt or mild pressor agents emphasizes the importance of not placing the fatalistic label of hardening of the arteries on such individuals

Attacks of syncope that are related to the upright position in patients with partial impairment of cerebral perfusion may be due to the pooling of large quantities of blood in the lower extremities particularly in the presence of large varicose veins and venous angiomas On the other hand the potential therapeutic importance of this observation is pointed out by the effectiveness of simple elevation of the legs in counteracting hypotension during surgery

Brief mention will also be made of the following cardiovascular phenomena that are related to changes in position and which are often over looked by clinicians

in addition to the murmurs created by the pulmonic stenosis and the septal defect, these blood vessels can also be productive of a continuous murmur in up to ten per cent of the patients[893b] Secondly, these hypertrophied vessels could give the impression of either normal or increased pulmonary vascular markings by x ray in up to one fourth of the cases[893c] (A similar situation may prevail bilaterally when the shunt is predominantly left to right, or unilaterally in the opposite lung field in the case of unilateral pulmonary atresia)

The importance of correctly diagnosing an uncomplicated tetralogy of Fallot is underscored by the fact that when it is not made—the most common mistakes being pulmonary valvular stenosis with a patent foramen ovale and cyanosis, a single ventricle with pulmonary stenosis, or transposition of the great vessels with pulmonary stenosis—the performance of an aortic-pulmonary shunt (the Potts procedure) is apt to induce cardiac enlargement and failure The current progress in the direct approach to the surgical correction of such lesions by open heart surgery with pump oxygenators and cardiac by pass techniques will also allow the surgeon to ascertain various complications of the tetralogy, the presence of which could preclude an otherwise satisfactory operative result[1, 87d, e] These include a marked overriding of the aorta and a persistent common atrioventricular canal (in place of the common type of interventricular septal defect)[893d]

ORTHOSTATIC HYPOTENSION AND OTHER POSTURAL CARDIOVASCULAR PHENOMENA

One of the most frequent situations for which the advice of a consultant physician is sought pertains to the evaluation of chest and cerebral complaints that are related to changes in the patient s posture A number of these conditions are discussed elsewhere in the text under aortic valvular disease (p 258), cerebral vascular accidents (p 360), carotid sinus syncope (p 293), angina decubitus (p 266), "abdominal angina" (p 300), drug induced postural hypotension—particularly with morphine (p 274), the potent hypotensive drugs (p 360), atropine (p 432), and nitroglycerin (p 274)—a ball valve thrombus or tumor of the left atrium (p 257), primary pulmonary hypertension (p 275), pulmonary embolism (p 212), dysautonomia (p 381), and other diseases that affect the autonomic nervous system Principally included among the latter are diabetes mellitus amyloidosis, and tabes dorsalis An orthostatic hypotension may be observed in patients whose hypertension is due to either a pheochromocytoma or an aldosteroma

Attention is directed to a comprehensive review of this subject by Silverman and Salomon[88a]

There is no substitute for the careful clinical evaluation of the effects of position in the course of a cardiologic examination One needs only to recall the following observations to be impressed with the scope of this maxim the accentuation of the presystolic murmur of mitral stenosis in the left lateral position, the accentuation of the murmur of tricuspid stenosis in the right lateral position the variation in intensity and shifting of peri

It should be borne in mind that malignant hypertension with prominent proliferative arterial lesions is occasionally encountered in young people in the absence of an underlying nephritis, and is particularly prone to be abrupt and fulminant in males and Negroes.[1274]

Since many patients with very high blood pressure levels are relatively asymptomatic, especially in the case of postmenopausal females, great care should be taken not to casually attribute recent dyspnea, dizziness, headache, easy fatigability, and other symptoms to this condition. This admonition is most noteworthy when the changes in the optic fundi due to lesions causing increased intracranial pressure are superimposed upon those of a pre-existing benign hypertensive retinopathy. The fully developed lesion of arteriovenous nicking is associated *only* with hypertensive disease. In fact, some cardiomegaly can be demonstrated in up to 95 per cent of the patients in which it is prominent.

The reader well appreciates the fact that over 85 per cent of hypertensive patients have "essential" hypertension. It will suffice by way of review and without elaborate discussion to enumerate the other causes of hypertension in the following abbreviated listing. The relationship of hypertension to each of these diseases is discussed and stressed elsewhere in this text under the individual entities. The various diagnostic studies which may be utilized in the study of patients with hypertension have been ably summarized by Hollander.[883b] This author also stresses the importance of differentiating between true arterial hypertension and the systolic hypertension that results from either an increased stroke output of the left ventricle (as occurs in heart block, aortic regurgitation, and the various causes of "high output" failure) or the decreased distensibility of the aorta which characterizes the arteriosclerotic involvement of this vascular structure.

1. *Parenchymal renal disease*
   - Glomerulonephritis (acute, chronic) (p. 0)
   - Chronic pyelonephritis (p. 110)
   - Congenital abnormalities (polycystic disease, hypoplasia, others) (p. 422)
   - Tumors (p. 332)
2. *Renal vascular disease* (arterial, venous)
   - Embolism
   - Thrombosis (p. 214)
   - Arteriosclerosis (p. 292)
   - Congenital defects (hypoplasia, aneurysm) (*vide infra*)
   - Dissecting aneurysm (p. 295)
   - Compression of renal arteries by an intrinsic or extrarenal mass
   - Arteriovenous fistula (p. 292)
3. *Diffuse vascular disease*
   - Polyarteritis (p. 307)
   - Visceral thrombophlebitis (p. 219)
   - Systemic lupus erythematosus (p. 304)
   - Coarctation of the aorta
4. *Endocrinopathies*
   - Pheochromocytoma (p. 21)
   - Cushing's syndrome (p. 28)
   - Pituitary tumors (acromegaly) (p. 30)
   - Hyperthyroidism (p. 18)
   - Aldosteroma (p. 29)
   - Arrhenoblastoma (p. 35)

1 The *syndrome of left lateral hypotension* describes the abrupt fall in blood pressure (and even a concomitant shock like state) that follows the assumption of this particular position [882b] The author has encountered this phenomenon *in a large* number of cardiac patients, and accordingly advises most of his patients suffering from heart disease to avoid the left lateral position This phenomenon presumably results from vasovagal reflexes that are induced by marked rotation and twisting of the heart, but may also be due to an obstruction at the *pulmonary veins or the left atrium* While this hypotensive state is most frequently noted in patients with enlarged hearts, dyspnea and precordial distress can also take place in individuals whose normal sized hearts demonstrate unusual mobility in the mediastinum This is particularly apt to occur when there has been a rapid and marked loss of weight in formerly obese people

2 In contrast to the aforementioned disorder, there is a *postural shock syndrome* that has been observed *in the latter part of pregnancy* which is corrected by the left lateral position This form of circulatory collapse is initiated or aggravated by the dorsal recumbent position It is probably due to the interference of venous return from the inferior vena cava by the pressure of the gravid uterus on this structure [88c]

3 *Postexertional orthostatic hypotension* has been described by Eichna, Horvath, and Bean in several instances of hypotension, shock, and even complete heart block with asystole following strenuous exercise [88d,e] It may occur in young and apparently healthy individuals

4 *Orthostatic hypernatremia* was mentioned earlier in this chapter, *with special reference to the potentiation of mercurial induced diuresis* by recumbency in patients with "refractory" heart failure (p 231) [810]

5 The number of *effects of posture on both normal and deranged electrocardiographic tracings and in the induction of arrhythmias* is legion [88] The electrocardiographic alterations can include changes in the P, QRS and T waves, changes in the P R and Q T intervals (including all degrees of heart block) stemming from the greater vagal influence during recumbency, and even the induction or disappearance of electrical alternans, left bundle-branch block and (posterior) myocardial infarction While sinus arrhythmia and extrasystoles tend to be more frequent in the recumbent position, orthostatic auricular or ventricular tachycardias might also be encountered, with or without an associated orthostatic hypotension [88f,g]

SYSTEMIC HYPERTENSION

If the potentially curable types of hypertension are to be recognized and treated, it would behoove all clinicians to regard systemic hypertension as but another possible manifestation of many generalized diseases [883] That this is a particularly important consideration in atypical cases of hypertension has already merited discussion under the endocrinopathies Furthermore, with the more prolonged observation of patients who have exhibited hypertension during the course of their pregnancy, it appears quite likely that the majority of patients with pre-eclampsia are candidates for the subsequent development of essential hypertension notwithstanding the normalization of their blood pressure in the puerperium [883a] This orientation may bear considerable prophylactic import

sive patients who lacked both a family history of the disease and convincing evidence to indicate another cause for the hypertension, (3) the development of an accelerated or malignant hypertension in elderly hypertensives, and (4) patients in any age group with essential hypertension of long duration whose disease abruptly became more severe The auscultation of a loud systolic bruit over the abdomen anteriorly and over the lumbar spine posteriorly in a patient with a persistent diastolic pressure of 170 mm of mercury or more should suggest a primary renal vascular lesion (Many of these patients also prove to have concomitant disease of the aorta in the form of thrombosis coarctation, or atherosclerotic plaque formation [897a, 911c] Neither the intravenous nor retrograde pyelographic studies may be very helpful in such situations

Several observers have independently been impressed with the degree of polyuria encountered in cases of unilateral renal hypertension [107] This manifestation is attributed to the physiologic activity stemming from the higher concentrations of renin and angiotensin that are demonstrable in the renal venous blood of such patients Partial visualization of the affected kidney may be noted on intravenous pyelography if enough renal tissue is still functioning on that side Marked leukocytosis and albuminuria are also very striking and of diagnostic value on occasion [107] Unilateral renal disease that is causing severe hypertension may be associated with a normal blood urea nitrogen (It is calculated that in the absence of dehydration, at least two thirds of the total renal functioning mass must be destroyed prior to the development of an elevation in this component [883b])

Ferris and Brust believe that the unusual TEAC blood pressure response (i e either a rise or no fall occurring) is a valuable screening device in patients with humoral forms of hypertension (including unilateral renal vascular lesions) whose hypertension is still curable [897] These observers were impressed by the incidence with which both the renal function and pyelographic studies proved to be nonrevealing and the rapidity with which malignant hypertension can develop in such patients Reference is also made in Section III of Part II to several promising methods of physiologically diagnosing significant unilateral renal disease in the presence of hypertension by an analysis of the urine coming simultaneously from each kidney (p 711) The use of "radiorenograms" (employing external scintillation counters and a radioiodine-labeled contrast medium) holds further promise in this regard *

THE CAROTID SINUS SYNDROME

I am frequently impressed both by the frequency with which the carotid sinus syndrome asserts itself clinically in a consultation practice and the infrequency with which this diagnosis is even considered by referring physicians The number of cardiovascular, neurologic, and metabolic disorders this condition may simulate is legion [889] Epilepsy cerebral vascular accidents, postural hypotension aortic stenosis hyperinsulinism Adams Stokes attacks narcolepsy, and Meniere's disease are the conditions most commonly so entertained

* See reference 88 of Part II

5 *Other significant causes of systemic hypertension*
Perinephric disease (infection, tumor hematoma) (p 109)
Obstructive uropathies (prostatism, aberrant vessels stricture)
Porphyria (p 61)
Polycythemia vera (p 188)
The diencephalic syndrome (p 544)
Increased intracranial pressure (p 363)
Lead poisoning (p 65)
Disease of the spinal cord (transection transverse myelitis tabes dorsalis)

One should not overlook the presence of hyperthyroidism in the hypertensive patient with an unexplained auricular fibrillation or tachycardia An "endocrine hypertensive syndrome," which appears to be closely related to the presence of adrenal cortical hyperplasia, and which requires differentiation from the true functioning adrenal tumors, is not infrequently encountered in women (It may ultimately be shown to bear a relationship to aldosterone secretion) This pseudo Cushing's syndrome is characterized by the quadrad of central obesity (often with a rapid weight gain), menstrual irregularities, a low concentration of sodium chloride in the sweat and hypertension [884] The urine may offer certain readily determined clues *that are of some differential importance when the possibility of adrenocorticogenic* hypertension is raised Namely, the urine of a patient with the Cushing syndrome does not have the low, fixed specific gravity or the persistently alkaline pH, both of which are so characteristic of primary aldosteronism (p 29)

Considerable emphasis should obviously be paid both to emotional factors and to technical artifacts in evaluating hypertension For example, it has been repeatedly shown that falsely elevated blood pressure readings are frequently obtained in very obese individuals due to the increased effort expended on inflating the sphygmomanometer [147] (In these very obese patients, determination of the radial artery pressure by either the auscultatory method or by palpation is more accurate The use of a wide cuff can also circumvent this difficulty) It is also known that a loosely applied *blood pressure cuff can result in a falsely elevated blood pressure reading* [885]

While *severe hypertension resulting from unilateral renal vascular occlusion* is unusual, it is nonetheless very important by virtue of its potential curability [886] The nature of the congenital malformation of the renal artery that may give rise to hypertension by interfering with the renal arterial perfusion varies It may take the form of either a hypoplastic vessel or a cirsoid angioma The diagnosis of arteriovenous aneurysms around the renal pelvis might be suspected by the finding of minute indentations of the ureter at its point of departure from the renal pelvis on the excretory urogram [886c]

Of 104 selected hypertensive patients who were studied by aortography at the Cleveland Clinic 30 were found to have focal disease of the renal arteries, the majority consisting of unilateral or bilateral arteriosclerotic plaques [886d] In six instances, a poststenotic aneurysmal dilatation of the renal artery could be demonstrated distal to the point of obstruction Selection of patients for aortography was based on the following indications (1) the finding of an unexplained disparity in the size or function of the kidneys by intravenous urography in a hypertensive patient, (2) young hyperten

static cancer neurofibromas, and lymphomas [897b, d] The very serious complications that may follow less than expert surgery on these tumors will be recounted in a later chapter (p 481)

SYNDROMES PRODUCED BY DISSECTING ANEURYSMS OF THE AORTA

Dissecting aneurysms of the aorta often deviate from their usual presenting clinical feature of sudden tearing chest pain in a hypertensive patient Various bizarre features and pain radiations may be experienced, depending on the site and course of the dissection and the organs involved [894] The variant syndromes and the diagnoses simulated are listed as follows

1 *Cardiovascular* Syphilitic heart disease, rheumatic heart disease, myocardial infarction, subclavian artery scalenus syndrome pericarditis, primary iliac or femoral thrombosis Look for a new aortic diastolic murmur and local diminished pulses developing Jaw pain also occurs in this condition

2 *Cerebral neurologic* Cerebral vascular accidents anterior spinal artery syndrome, hypertensive encephalopathy [895]

3 *Pulmonary* Pneumonitis pulmonary infarction, mediastinal tumor Suspect a dissecting aneurysm in the presence of an acute left hemothorax and air hunger

4 *Abdominal* Bleeding peptic ulcer acute pancreatitis, mesenteric thrombosis acute cholecystitis Malignancy may also be considered if an aortic mass with but little pulsation is felt

5 *Renal and Retroperitoneal* Renal calculus or infarction, hematuria uremia shock Look for the development of abdominal or lumbar ecchymoses

It should be remembered that this disease can affect individuals in their second and third decades, particularly in association with pregnancy, coarctation of the aorta and other congenital heart diseases Dissecting aneurysms of the thoracic aorta and saccular aneurysms of the abdominal aorta have also occurred in association with polycystic disease of the kidneys and liver [141b]

It is emphasized that extensive and repeated dissection can occur without pain (The pain associated with a dissecting aneurysm appears to be related more to its impact upon the surrounding tissues than merely the dissection of the intima from the media of the aorta) In this regard however, it must be appreciated that while only 51 per cent of the 85 patients with dissecting aneurysms observed by Baer had chest pain many were admitted in states of shock confusion or coma [894] Another important point for clinicians to recall is that a significant number of these dissections have occurred in the absence of hypertension Some authorities are pondering whether a possible relationship between the use of potent antihypertensive therapy and the subsequent development of a dissecting aneurysm might exist

The concept has gradually evolved that cystic medial necrosis of the aorta may represent a nonspecific result of hemodynamic stress on the

The carotid sinus response should be ascertained in *every* patient presenting with recurrent and unexplained dizziness, weakness, angina pectoris, tinnitus, and seizures of all descriptions, with or without preceding aurae (The right carotid sinus is more commonly dilated and sensitive than is its counterpart on the left) Suspicion should also be roused when these symptoms occur in elderly male patients with associated arteriosclerotic or hypertensive heart disease, and when they are related to either the upright position or to changes in the position of the head and neck It is cautioned, however, that a hyperactive carotid sinus reflex is *not* synonymous with or diagnostic of the clinical syndrome The wide variety of electrocardiographic changes and symptoms that can be induced in normal, active individuals following carotid sinus stimulation underscores the rigid clinical criteria that must be adhered to in diagnosing the hypersensitive carotid sinus syndrome [890]

A number of pertinent observations concerning the overexcitability of the carotid sinus mechanism are of considerable clinical interest When associated with the presence of biliary tract disease, this hypersensitivity has been noted to disappear after a cholecystectomy [891a] Emotional factors may also play a considerable role in the activity of the carotid sinus, even at nonhypoglycemic levels [891b] Contrary to the general impression, cardiac syncope in the presence of auricular fibrillation is not infrequently due to a hyperactive carotid sinus mechanism In fact, this state can be potentiated by the action of digitalis [892] It is important to appreciate these considerations inasmuch as the prognosis may not be quite as serious in carotid sinus mediated syncope as in the other types of cardiac syncope Furthermore, therapy with the vagal blocking drugs and local irradiation have proved to be very beneficial

On rare occasions, *chemodectomas* (also known as nonchromaffin paragangliomas carotid body–like tumors, and receptomas) are encountered, primarily arising from the carotid body or glomus jugulare In a review of more than 1000 cases of tumors involving the neck and parotid areas seen at the Lahey Clinic, 32 instances of carotid body tumors were encountered [897d]

The three types of carotid body tumors usually recognized include those wherein the normal structure of the carotid body is simulated (the most common variety) those giving an adenoma like appearance, and the angioma like type [897b] At times the features of all three can be identified throughout certain tumors While these tumors are usually benign, they may metastasize locally to the bone, the lymph nodes, and intracranially It is now estimated that local, regional or distant metastases occur in approximately 15 per cent of these neoplasms

Chemodectomas are usually characterized by their unilateral nature and their slow growth as a painless mass in the side of the neck for months or years Symptoms may result from encroachment upon the pharynx, involvement of the surrounding nerve structures, or the referral of pain to either the neck or the ear Unusual carotid sinus sensitivity and other symptoms suggesting altered chemoreceptor activity and vagal dysfunction have been described [897]

The differential diagnosis usually includes branchial cleft cysts, meta

the ascending aortic arch in the absence of a luetic aortitis, but only infrequently so on the anterolateral wall of the ascending aorta The former are rarely observed in the posteroanterior chest film, however, inasmuch as their posteromedial location is overshadowed by the spine [900] This contrasts with the situation in a luetic aortitis wherein the intimal calcification occurs throughout the entire circumference of the ascending aorta

It is wise to consider the possibility of an *unperforated aortic sinus aneurysm* when faced with a loud systolic murmur and a fusiform or saccular dilatation of the ascending aorta [901] Angiocardiography has aided in establishing this diagnosis [901c] The right aortic sinus is most frequently involved with the posterior (noncoronary) aortic sinus being the next one in order so affected

Aneurysms of the aortic sinuses of Valsalva have been associated with syphilis, subacute bacterial endocarditis, arteriosclerosis, and cystic medial necrosis, or they may be due to a congenital weakness in the wall of the heart at the base of the aorta Associated congenital defects have included high ventricular septal defects coarctation of the aorta, arachnodactyly, and bicuspid aortic valves In fact aneurysmal dilatation of the aortic sinuses may be demonstrable in infants and children with Marfan s syndrome long before the other stigmata of this disorder are prominent (Steinberg and his colleagues have reported upon identical twins two years of age, with this condition who were found to have cardiac enlargement and murmurs The dilatation of the aortic sinuses could be readily demonstrated on angiocardiography)[901d] The aortic leaflets, above which rupture of one of the sinuses of Valsalva perforates are usually normal, however In contrast to congenital aneurysms of the sinus of Valsalva leutic aneurysms involving this area may be huge and can occasionally rupture outside the heart

A variety of clinical syndromes may ensue resulting from such complications as rupture (the most common one), pressure phenomena, endocarditis and septic embolism Depending on the location of the aneurysm, rupture has been observed to occur into the right ventricle the pulmonary artery the right atrium the left ventricle or the pericardial sac When rupture takes place there is usually sudden dyspnea palpitation and collapse, associated with a continuous machinery like murmur along the left sternal border due to the creation of a cardiao-aortic fistula

As was pointed out above the acute refractory right heart failure resulting from this fistula and the ensuing left to right shunt has already proved to be susceptible to repair by open heart surgery both before and after perforation [901 e] A saclike structure may be found which can be resected

Most of the reported *aneurysms of the coronary arteries* have occurred in adults Exceptions are to be found however, in the mycotic embolic variety, those associated with rheumatic carditis, and those related to polyarteritis or some other form of necrotizing arteritis which can also affect infants and children [90] Furthermore, there is probably a congenital type inasmuch as other congenital malformations of the heart are usually concomitantly noted in infants with this disorder

Arteriosclerotic aneurysms of the thoracic aorta can produce unusual

aorta. For example, McKusick, Logue, and Bahnson have described four patients with disease of the aortic valve (stenosis and regurgitation) in whom diffuse aneurysms of the ascending aorta developed—with or without dissection—in association with the histologic presence of this change.[896e] Similarly, the background of either essential hypertension or a congenital aortic stenosis in patients with dissecting aneurysms, possibly with a genetic inferiority of the aortic media (as is best exemplified by the Marfan syndrome) is well known.[896f]

The term "dissecting hematoma" is probably more accurate since the condition is not an aneurysm, but rather a progressive splitting of the medial layer of the aorta by the hematoma.[896a] As surgical techniques continue to improve, it will become increasingly important to estimate both the site and the extent of the initial tear and dissection. The presence of simultaneous pain in the back and epigastrium favors the aortic arch or a site just below the left subclavian artery. The development of an intense murmur of aortic insufficiency usually places the tear within a few centimeters of the aortic valve. Other signs that might point to this lesion include a pulsation of the right sternoclavicular joint, and a friction rub in the upper parasternal areas that is synchronous with the heart beat.

Thoracic surgeons with extensive experience have noted that dissecting aneurysms are occasionally chronic, and that they may go unrecognized for many months until a fresh dissection has occurred.[896b, c] Prior, Buran, and Perl reported upon five fatal cases of *chronic (healed) dissecting aneurysms* in which the survival time ranged from 63 days to several years.[896b] The pathologic changes were observed to vary from imperfectly organized intramural hematomata to secondary endothelial lined channels (double barreled aortas) with abundant elastification and pronounced proliferative changes in the intima and subintima.

SYNDROMES PRODUCED BY NONDISSECTING ANEURYSMS OF THE AORTA

The long asymptomatic course of some patients with *aneurysms of the thoracic aorta*, usually of luetic origin, has been impressive. The occasional rupture of an aortic aneurysm into the superior vena cava, the pulmonary artery, the pericardial cavity, the pleural cavity, the right auricle or ventricle, and other sites may be followed either by sudden death or by survival for various durations. The divers manifestations so produced—particularly the variants of the superior vena caval syndrome and right sided heart failure—are well reviewed in several recent reports.[898, 899] The recognition and differentiation of these complications from those of nonsyphilitic dissecting aneurysms and from the sequelae of myocardial infarction might prove to be quite difficult. As in the case of dissecting aneurysms, the diagnosis of thoracic aortic aneurysms is no longer solely an academic matter since their excision is now feasible and the fistulous communications correctible by surgery. Moreover, early successful surgical repair has also proved to be feasible in cases of traumatic arteriovenous fistula of the aorta and the superior vena cava.[898c]

Calcified atheromatous intimal plaques are not uncommonly found in

Several further comments are in order concerning this particular sign The accurate assessment of expansile pulsation is best achieved by palpating the mass at two points or by visualizing the mass at two points during fluoroscopic examination Nevertheless even with these precautions, it may be difficult to differentiate an aneurysm (or a highly vascular tumor) from either an upper abdominal mass which is transmitting aortic pulsations or from an abnormally tortuous aorta A lateral view of the abdomen might demonstrate the presence of calcification in the wall of an aneurysm when this structure cannot be palpated with accuracy in an obese abdomen While calcification of the abdominal aorta is common and usually bears no diagnostic significance, its presence in a patient with recent unexplained back pain might profitably direct one s thinking towards an underlying aneurysm or dissection of this vessel

Splenic artery aneurysms are probably not as rare as one might surmise from the literature Prior to rupture the most common complaint is pain in either the epigastrium or the left upper quadrant Splenomegaly has been noted in almost one half of the reported cases The diagnosis is usually made clinically, however, by the demonstration of an oval or round ring of calcification in the left upper quadrant At times, calcium deposits are seen in the splenic artery *itself* The extraordinary association of pregnancy with rupture of these aneurysms is well documented Their greater incidence in females—in contrast with the male preponderance in most other types of aneurysms—is also noteworthy Rupture may take place into the greater or lesser sacs the retroperitoneal space, the stomach, the colon, or the pancreas [907]

A few cases have been described in which an acute bacterial infection was engrafted on the aortic wall at the site of atherosclerosis, with rupture ultimately occurring at the site of the ensuing *mycotic aneurysm* This may take place either as a result of an underlying endocarditis[909] or in the absence of such a centralized emboligenic focus [910] In the presence of an aneurysm of the aorta of obscure etiology with or without calcification of the mesenteric nodes, the possibility of a mycotic aneurysm resulting from either a tuberculous para aortic lymphadenitis or a tuberculous aortitis might also be entertained [543]

ANOMALIES AND DISORDERS OF THE GREAT ARTERIAL TRUNKS

In light of the recent advances in vascular surgery, the diagnosis of a *chronic thrombosis affecting the terminal abdominal aorta and the iliac vessels* (the Leriche syndrome) merits added emphasis [911] Intermittent claudication and easy fatigability referable to the thigh and the hip, diminished pulsation of the femoral arteries and at times of the abdominal aorta, thrombophlebitis impotence a loud systolic bruit over the abdominal aorta and lumbar spine area, and other symptoms referable to the extension of the occlusion to the inferior mesenteric and renal arteries—or any combination of these features—may characterize the clinical complex This syndrome constitutes one of the bona fide indications for translumbar aortography especially when resectional surgery is contemplated (p 783)

Edwards has pointed out that the location of claudication pain is

manifestations, particularly when the concavity of the arch is involved In the elderly and hypertensive, aneurysms of the thoracic aorta (particularly those affecting the arch and the descending portions) are tending to be arteriosclerotic rather than luetic with increasing frequency The presenting features can be manifold These could include the finding of mediastinal or hilar masses, backache (due to the erosion of the bodies of the dorsal vertebrae), hoarseness (due to recurrent laryngeal nerve paralysis), hemoptysis (due to an erosion or stenosis of a large pulmonary artery), or *epigastric pain In fact, such signs as hoarseness, severe clubbing, and profound* weight loss might be readily misconstrued as signifying a metastasizing bronchogenic carcinoma or a mediastinal mass

The presence of a dense clot in the arteriosclerotic aneurysm of the thoracic aorta accounts for the absence of pulsations and the failure of the aneurysm to be visualized by angiocardiography in certain cases [903] Steinberg noted pulsatile movements of the aneurysm in only one of six patients [903a] He points out the definitive diagnostic value of angiocardiography in many of these cases, particularly in its differentiation from a chronic dissecting aneurysm (which concomitantly produces a large vessel and widespread narrowing of the lumen)

The widening of the superior mediastinal shadow in the region of the aortic arch following injury to the chest—even after a prolonged latent period with a nonpenetrating injury, and unaccompanied by rib fractures—should suggest an incomplete *traumatic rupture* of either the aorta or another great vessel An aneurysm could eventually develop at such a site [904] Patients with chronic traumatic aneurysm of the thoracic aorta can remain asymptomatic and gainfully employed for many years after the partial rupture Accordingly, surgical correction should not be attempted too hastily for these individuals in the absence of symptoms or evidence of enlargement of the aneurysm, notwithstanding the availability of resectional and grafting techniques [904e]

A number of observers have been impressed with the increasing frequency of *arteriosclerotic abdominal aneurysms* and their ability to simulate a host of other disorders, particularly lesions within the urinary tract [905] While various descriptions of pain are presented (frequently suggestive of renal colic), up to one half of these patients *have no significant pain* Reference was made in an earlier chapter to the ability of a ruptured atherosclerotic aneurysm to manifest itself for several weeks in the form of unexplained fever and leukocytosis (p 107) [332] Very few abdominal signs may be present in this situation Ileus is another relatively frequent finding [906]

There may be an interval of days to weeks from the onset of leaking to the final rupture, in large measure due to the tamponade effect exerted by the tensed retroperitoneal tissues The progressive anemia, the increased soft tissue mass surrounding the calcified aneurysmal wall, and the obliteration of the psoas shadow can alert the clinician to initiate surgical therapy [906b]

The presence of a truly expansile and tender mass is diagnostic, the latter feature helping to differentiate it from a buckled arteriosclerotic *aorta* It may be difficult, however to detect the presence of an expansile pulsating mass in an obese individual with an abdominal aortic aneurysm

of the descending aorta beyond the right heart border before it re-enters the left hemithorax is very apt to simulate a mass projecting from the mediastinum into the right lower lung field in the posteroanterior chest film [913] The mechanism producing this "S" curve can be better appreciated when it is realized that the descending aorta is quite mobile except at its point of exit through the diaphragm

Attention is directed to three additional entities which are not infrequently confused with aneurysms

Buckling of the common carotid artery is usually found on the right side of the neck in elderly hypertensive, and arteriosclerotic female patients [914] If the clinician is not aware of this cause of a distinct large pulsatile mass in the neck, it will undoubtedly be regarded as an aneurysm The absence of associated signs and symptoms of pressure on the adjacent structures—along with the absence of involvement of the innominate artery or aorta in a patient over forty with such a tumor in the right neck—should influence the clinician against the diagnosis of an aneurysm

Buckling of the internal carotid artery can appear as a symptomless pulsating bulge in the lateral part of the pharynx While it is usually accounted for by an arteriosclerotic widening and dilatation in the elderly, it may represent a developmental abnormality in the young [914b]

Buckling of the innominate artery is similarly due to the elongation tortuosity, and dilatation of this particular vessel [915] It also occurs in hypertensive, arteriosclerotic individuals in whom no evidence of tertiary syphilis can be found In view of the right superior mediastinal prominence it exhibits radiographically, the condition may simulate an aneurysm either of this vessel or of the aorta, a superior mediastinal tumor, a retrosternal thyroid, lymph node enlargement and disease within the apex of the right lung When further doubt still exists angiocardiography can delineate this buckling phenomenon very nicely [916] This technique not only eliminates the necessity for an exploratory thoracotomy, but also obviates potential serious damage to vital vascular connections resulting from the thoracic surgery In some cases there is a tendency for the buckling to disappear with correction of the hypertension [914b]

The *persistence of a left superior vena cava* can likewise simulate either a widened aorta or a mediastinal mass [917] It may or may not be associated with complex cyanotic types of congenital cardiovascular disease This structure has also been positively identified by angiocardiography It is pointed out that the left arm veins should be used to inject the contrast media when this particular anomaly is suspected

The uncommon syndrome of *chronic obliteration of the great arterial trunks* originating from the aortic arch (the innominate the left common carotid, and the left subclavian arteries) is usually due to an arteritis of unknown origin which affects the media of both the aorta and its branches Syphilitic aortitis atheromatosis, chronic dissecting aneurysm, thrombophilia, and chest trauma have also been implicated in several of the reports Some authors have felt this disorder (Takayashu s syndrome) may represent the result of a hyperergic reaction of structures exposed to hydrodynamic stress They have even related it to rheumatic or rheumatoid disease and to the cranial arteritis of Horton Occlusion of the subclavian

often (but not always) an aid in determining the proximal level of an arterial occlusion (i e , foot pain with plantar or tibial artery obstruction, calf pain at any level from the tibial arteries upward, pain in the thigh adductors in deep femoral artery *occlusion, one-sided hip or buttock pain* with hypogastric artery occlusion, and bilateral pain when the obstruction involves both hypogastric arteries or the aortic bifurcation)[911d] In the presence of palpable pulses, claudication usually indicates a *selective occlusion* involving the branches of a main stem artery supplying the affected muscles In addition to oscillometry and arteriography under this circumstance, the auscultation of a loud systolic murmur over the area of greatest narrowing has been particularly valuable in establishing the diagnosis of localized occlusions involving the aorta and the iliac or femoral arteries

The discovery of diabetes mellitus in a patient with the Leriche syndrome is extremely important in view of both the frequency of distal ischemic manifestations and the much higher incidence of other clinical atherosclerotic lesions[911e]

In a patient exhibiting evidence of severe arteriosclerosis and hypertension, the presence of periodic abdominal pain with bloatedness and dyspepsia might be due to *"abdominal angina"* resulting from the concomitant mesenteric vascular involvement[908] Sedlacek and Bean and *others have observed that abdominal "angina" produced by intermittent* ischemia of the mesenteric arterial circulation may be suspected from the following combination (1) persistent and consistent abdominal pain that occurs regularly within thirty to sixty minutes after eating, and (2) alleviation or moderation of the pain that can be produced by the patient's lying in some special position on the belly or side, or by leaning forward in the sitting position[908] The relief afforded by the latter maneuver—heretofore always regarded as being quite characteristic of pancreatic and other retroperitoneal tumors—results from the reduction in the drag on the mesentery which in turn relieves this added mechanical *impediment* to the blood flow

Kinking or buckling of the aortic arch is a developmental anomaly which is important because of the frequency with which it is mistaken in *posteroanterior roentgenograms for one of the following* coarctation of the aorta, pulmonary or mediastinal tumors, aneurysm of the thoracic aorta, and organic heart disease[912] The "kink' in the aortic shadow is best seen in the lateral and left anterior oblique positions with its angular convexity in the region of the ligamentum arteriosum The latter structure presumably does not stretch or degenerate with the unfolding of the aorta, and subsequently exerts traction on this vessel at that site Such designations as "pseudocoarctation" and "subclinical coarctation" are misleading inasmuch as this condition bears no relationship to true coarctation Since most of these *patients exhibit systolic murmurs at the base* of the heart (9 out of 10 in one series)—probably due to the turbulence of the blood flow in the area of the "kink"—it may be necessary to resort to angiocardiography for a final clarification of the underlying process

Dextroposition or buckling of the descending thoracic aorta is likewise due to a tortuous arteriosclerotic aorta Syphilis and a congenital right sided descending thoracic aorta have also produced a similar picture The sweep

GROUP X

Dyscollagenoses

General Considerations
Disseminated Lupus Erythematosus
Polyarteritis (Periarteritis Nodosa)
Dermatomyositis
Diffuse Progressive Scleroderma
Scleredema Adultorum
Relapsing Febrile Nodular Nonsuppurative Panniculitis
Rheumatic Fever
Rheumatoid Disease
Atypical Arthritis in Systemic Illnesses
Palindromic Rheumatism
Erythema Nodosum
Chronic Polyserositis
Pick's Disease
Chronic Hyperplastic Perihepatitis
Concato's Disease
Elastica Disease
Epidermolysis Bullosa
The Ehlers Danlos Syndrome

GENERAL CONSIDERATIONS

IT HAS BEEN most interesting to observe the emergence of this group of diseases from the status of frank pathological curiosities to a rank of sufficient importance to merit at least one paper dealing with their manifold aspects in practically every current journal In terms of diagnostic acumen here in particular revelation comes to the prepared mind This significant change has been wrought by such factors as the more clear cut

and carotid arteries may also occur in the thoracic outlet syndrome because of the trauma to these vessels In the case of the former, claudication after exercise is manifested by aching in the left shoulder and neck

The clinical picture may consist of carotid sinus syncope, intermittent claudication *of the masticatory muscles, eye changes (visual disorders,* amaurosis, cataracts, iris atrophy, and corneal opacities), weakness and numbness of the upper extremities, absence of the radial and carotid pulses with concomitant hypertension in the legs (*"pulseless disease"* or *"reversed coarctation"*), nasal septum perforation, arterial insufficiency in the brain, and epileptiform seizures The collateral channels have even produced erosion ("notching") of the ribs [918, 91] In a number of the reported cases, a loud continuous systolic and diastolic murmur was heard anteriorly at the base of the neck This bruit has been shown to result not only from the narrowing of the main artery, but also from the involvement of those regional arteries which would ordinarily supply the collateral circulation [91]

The diagnosis of "pulseless disease" is not solely an academic matter since surgical correction of the cerebral vascular insufficiency induced by this disorder is quite possible In fact, there already are several recorded instances in which an endarterectomy or a resection with the use of either a by-pass homograft or a nylon aortic substitute has restored the highly important arterial perfusion to the brain [92] An endarterectomy for partial occlusion of the internal carotid artery is often effective because of the short obstructions that are frequently present

There may be much overlapping in both the pathologic and the cerebral manifestations of pulseless disease and the more common syndrome of carotid artery thrombosis in which the subclavian vessels show no apparent involvement The internal carotid artery can be palpated in *the neck only with difficulty* Catheter *arteriography* has proved to be the best method for studying the aortic arch and its main trunks, enabling one to focus attention individually on each major vessel While aortography is not essential in localizing the obstruction in the aortic area, considerable aid can be obtained from ophthalmodynamometry (p 809), electroencephalography (with and without manual occlusion of the cervical carotid pulse), and carotid arteriography performed distal to the block

Every so often, clinicians and pathologists encounter patients with *extraordinary degrees of atheromatosis in whom practically* all the major vessels are affected One recent report cites such an instance in which the arteries to all four extremities and the head were partially or completely occluded, resulting in the coexisting features of the Leriche syndrome the aortic arch syndrome, and marked cardiac hypertrophy [90]

Pulseless disease has masqueraded as both a patent ductus arteriosus (because of the aforementioned murmur) and coarctation of the aorta (because of the occlusion of the left subclavian artery and even the more distal aorta) *A number of these individuals have also had occlusive lesions* in the large arteries going to the lower limbs which require endarterectomy

In fact Dubois has placed its incidence as one-half that of acute rheumatic fever at the Los Angeles County General Hospital [9 5] In most centers the incidence of disseminated lupus erythematosus encountered is much greater than that of polyarteritis—the difference often amounting to tenfold

One should bear in mind the variable course of this disease and the fact that it may be present for long periods and without any cutaneous eruption before a positive L E test is found Its chronicity is often demonstrated by the presence of some single manifestation (as anemia arthritis, or purpura) for up to twelve years before other features of the condition become apparent This test may be positive only during exacerbations, however

Many clinicians have been impressed with the frequent wide overlapping in both the clinical features and laboratory findings of systemic lupus erythematosus and rheumatoid arthritis including positive L E and sheep-cell agglutination tests Accordingly the L E cell phenomenon must be regarded as a frequent nonspecific finding in the latter disease (having occurred in 25 of 91 patients in one series), and the diagnosis of systemic lupus erythematosus must not be made unless other diagnostic criteria coexist This consideration is most apt to arise in the presence of rheumatoid nodules, Felty s syndrome and hypergammaglobulinemia [926]

It should be pointed out that the last word has not yet been said concerning the best method of performing the L E cell test (see Section I of Part II, p 671) It is currently felt that by employing at least three variations (i e , utilizing two concentrations of heparin as the anticoagulant a clotted method and the Snapper ring technique) a suspected case of lupus can be more adequately screened [940] In most instances however even though the patient enters a remission, the L E diathesis still exists The L E cell phenomenon has been reported in multiple myeloma, pernicious anemia in relapse, moniliasis, hematogenous tuberculosis dermatitis herpetiformis during cortisone withdrawal and transiently in erythema solare and hypersensitivity states (Apresoline, Dilantin, and penicillin reactions) [9 7] Similarly, before committing himself to the diagnosis of lupoid hepatitis the clinician must be aware of the fact that patients with classic cirrhosis or viral hepatitis often experience symptoms referable to their skin and joints, and that liver disease *per se* might be responsible for false-positive L E cell tests [9 7a]

Several excellent reviews dealing with the manifold clinical constellations of this disease have appeared in the recent literature prompted in large measure by the interest engendered by the L E cell test [9 8, 930] In addition to those manifestations recounted in the introduction to this section the patient may present with fever weight loss pericarditis pleuritis, a variety of pulmonary lesions [932] kidney involvement,[931] convulsions [933] adynamic ileus (particularly affecting the duodenum and jejunum) other gastrointestinal symptoms [934] polyneuritis [933b] and Raynaud s phenomenon Small fluffy white spots in the nerve fiber layer of the retina known as 'cytoid bodies occur in one out of four patients (They may also be seen in other diseases)[9 8]

From the above enumeration of its signs and symptoms it is not difficult to appreciate why this disorder has often been initially diagnosed

pathological and clinical perspectives, the development of better diagnostic techniques, the frequent use of drugs known to elicit the e nonspecific bodily reactions (sulfonamides, gold, hydrazinophthalazine), and the availability of effective therapy (hormones, chloroquine) Reference was made earlier to the "panmesenchymal" and "panangiitic" reactions that can take place in certain susceptible individuals with rheumatoid arthritis, either while being kept on a high maintenance dosage of cortisone and its analogs, or as these hormones are being withdrawn from them (p 14)[17]

In view of the widespread distribution of collagen, one must consider *the possible presence of those diseases which alter this network in patients with* unexplained arthritis, polyserositis, cardiorenal disorders, hypertension, and atypical skin, ocular, and pulmonary changes of all types[9.3, 9.4, 978] Only a few of the interesting and pleomorphic variants of this already sizable group can be discussed here Several of the syndromes and diseases resulting from hypersensitivity reactions bear considerable clinical similarity to the dyscollagenoses, especially "allergic vasculitis" Since these have been discussed previously at some length under Groups II (p 62) and VIII (p 225) they will receive no further comment in this chapter

Unfortunately, the term "collagen disease" has received exaggerated popularity since it was initially coined by Klemperer in 1942 Indeed, this designation is not infrequently being currently used as a catch *all cliché* in diagnostic desperation It might possibly be equally correct to refer to these diseases as "the nonrheumatoid connective tissue disorders," according to a suggestion by Talbott[9.30] At this point, therefore, it is quite in order to review briefly a few basic concepts for purposes of general orientation

Collagen tissue is composed of collagen fibrils and a ground substance which serves as the binding framework in the synovial and serous membranes the endocardium, and the walls of the blood vessels Pathologic changes in the connective ti sue may occur consisting either of necrosis, or fibrinoid degeneration, cellular proliferation and infiltration, and tissue *sclerosis if the injury is less intense*[9.4] *A widespread* vasculitis can also take place in the smaller vessels While "fibrinoid" material resembles fibrin with the usual stains, it differs in its ability to take the metachromatin stain Fibrinoid is *not* specific to this group of diseases, however, since it may be found in many other disorders and lesions, such as malignant hypertension and peptic ulcer

The pathologists and clinicians interested in these "group diseases" constantly stress the fact that the histopathologic similarities and clinical overlapping do not necessarily imply etiologic or pathogenetic identity Nevertheless, one cannot fail to be impressed with their close resemblance to the "diseases of maladaptation' which have been produced nonspecifically in experimental animals by Selye and others in response to a wide variety of stressors (p 353)

DISSEMINATED LUPUS ERYTHEMATOSUS

Since the availability of the L E cell test the correct diagnosis of disseminated lupus erythematosus has been made much more frequently

globulin elevated in systemic lupus, but positive heterophile, Coombs, and cold agglutination tests may also occur The prolonged periodic observation of "chronic biologic false-positive reactors is obligatory if one is to institute prophylactic therapy and to lengthen the periods of remission (p 155)[654] A persistent leukopenia (even in the presence of infection) with few lymphocytes, a hemolytic anemia, or a purpuric syndrome suggesting an idiopathic thrombocytopenic purpura may be present[937] Eosinophilia is unusual, however Dameshek and Reeves have made the very sobering observation that following splenectomy on three patients exhibiting either an autoimmune hemolytic anemia or 'idiopathic thrombocytopenic purpura, the overt manifestations of disseminated lupus erythematosus first appeared[938] Since the L E cell tests had been negative prior to the splenectomy—along with few symptoms actually referable to lupus—it was inferred that the intact spleen exerts a controlling influence on this disease

A peculiar sensitivity to infection has long been recognized in lupus and must be constantly borne in mind when intensive steroid therapy is instituted Tumulty has emphasized that it is important not to overlook a superimposed treatable infection—particularly of the heart valves or kidneys—in the patient afflicted with systemic lupus erythematosus[939] There appears to be little effect of an acute or subacute disseminated lupus *erythematosus on viable infants borne by mothers who harbor these disorders* Temporary subjective and even laboratory remissions may be induced by pregnancy, but the basic process is generally not altered[941] This aspect of the disease is by no means fully comprehended inasmuch as placental transmission of the L E factor and a familial occurrence of disseminated lupus erythematosus have both occurred[94 b]

POLYARTERITIS

Polyarteritis (or periarteritis) poses many of the same considerations as disseminated lupus erythematosus[943] It has several of its own features, however due to the necrotizing inflammatory and obliterative processes *involving the smaller arteries, arterioles and occasionally the veins* Nodose lesions of macroscopic size are actually quite rare They should still be sought for if a muscle biopsy is anticipated inasmuch as the value of this procedure is enhanced by using such a site (p 796)[944]

The pleomorphic clinical picture might variously center about the eosinophilia polymyositis hypertension gastrointestinal complaints (often the diagnosis is first suggested by the pathologist s report of an appendix or gallbladder) primary liver disease[945] asthma, interstitial keratitis with bilateral deafness (Cogan s syndrome),[946] polyneuritis,[947] myocardial involvement secondary to a coronary arteritis,[945] or the renal manifestations When the proctoscopic examination is not remarkable in the presence of a suggestive ulcerative colitis the diagnosis of polyarteritis should be entertained

Retinal detachment can occur in periarteritis in which case it may be due to a choroidal periarteritis or an albuminuric retinitis Other ocular manifestations in this disease consist of retinal perivasculitis, occlusion of the central retinal artery, episcleritis, iritis and nodular scleritis

as rheumatic fever, rheumatoid arthritis, idiopathic thrombocytopenia, Raynaud's disease, glomerulonephritis, virus pneumonia, epilepsy, scleroderma, a drug reaction, and bacterial endocarditis Similarly, systemic lupus erythematosus has presented itself as a surgical problem in the form of bleeding from the gastrointestinal tract, abdominal pain, mesenteric thrombosis, pancreatitis, and even rupture of the colon [934a] The clinician must not be misled by the histologic report of "hyperplasia" or other non diagnostic features in the presence of unexplained and persistently en larged superficial lymph nodes, but should closely observe these patients for the appearance of malignant and collagen diseases A large number of these individuals will ultimately prove to have disseminated lupus ery thematosus This diagnosis might be suspected by the alert pathologist from the histologic examination of the lymph nodes (i e , a characteristic hyperplasia in which plasma cells with PAS positive cytoplasm and PAS positive inclusions are prominent) [934b]

The presence of a marked splenomegaly, hepatomegaly, or ulcerations of the skin and mucous membranes should direct an etiologic analysis along lines other than lupus The history of overexposure to sunlight or to ultra violet radiation preceding the onset of symptoms has occasionally alerted the clinician to lupus In this respect, it should be borne in mind that sun light can also precipitate the manifestations of other diseases, including porphyria and poikiloderma vasculare atrophicans (p 559) The latter is a pigmented, atrophic, and telangiectatic erythroderma that tends to affect the trunk, the axillary folds and the flexor aspects of the extremities The minimal renal findings (hematuria, cylindruria, proteinuria), the frequent recurrence of pneumonitis, and the remission following discontinuation of the drug serve to differentiate the hydralazine syndrome from classic lupus erythematosus [935] While it has been suggested that the patient with lupus is an unusually potent antibody producer, the nature of the antigen has not yet been fathomed, except possibly in the cases of Apresoline and Dilantin

It must be appreciated that the current classification of lupus erythematosus is an arbitrary one, with many transitions existing between the localized discoid or generalized discoid forms and the classical systemic symptom complex In a survey of 192 dermatologists, Reiches has collected 353 cases of discoid lupus that were followed by systemic lupus erythema tosus over periods of time ranging from months to many years, including three such patients under his own observation who manifested systemic involvement six ten, and thirteen years after the discoid lesions [936a] Dubois and Martel have shown that if one combines the positive features in the history, the significant physical findings, and the laboratory abnormalities evidence of systemic involvement can be found in up to 96 per cent of patients with chronic discoid lupus (an extraordinarily high percentage to this author) [936b] None of the patients with the latter disease however, exhibit pleural effusions, ascites, fundic lesions central nervous system damage, or splenomegaly

The cutaneous manifestations of acute disseminated lupus erythematosus are depicted in Figure 68 (Atlas page 43)

Not only are the serologic tests falsely positive and the serum gamma

DIFFUSE PROGRESSIVE SCLERODERMA

In an evaluation of both the medical and surgical treatment in 38 cases of diffuse progressive scleroderma seen at the Lahey Clinic my colleagues were impressed with the frequent and profound involvement of many systems of the body [959] In addition to the typical skin changes lesions of the gastrointestinal tract the lungs, the larynx the heart multiple peripheral nerves, and the joints were encountered as has been the experience of others who have studied this disease [960 963] Scleroderma has simulated ulcerative colitis [172]

The cutaneous manifestations of generalized scleroderma are depicted in Figure 70 (Atlas page 44)

The concept of *scleroderma heart disease* has been generally accepted following its classic description by Weiss and his colleagues [964] *Scleroderma renal disease* has recently received some attention as a clinical entity being manifested by hypertension, renal failure, and the presence of urinary albumin red cells, and casts [965] The likelihood of scleroderma renal disease is all the more feasible in the patient with scleroderma who rapidly develops a malignant type of hypertension [965d] Its significance is enhanced by the observation that rapid deterioration has ensued in a number of these cases *following the administration of cortisone*

Several clinicians have observed the development of scleroderma following prolonged periods of great anxiety [966] They have invoked the con cept of a stress maladaptation phenomenon to explain this association Another interesting but unusual association has been that of scleroderma and various lung cancers (bronchogenic carcinoma and alveolar cell' carcinoma) in four patients [967]

SCLEREDEMA ADULTORUM

Scleroderma should not be confused with scleredema adultorum (Buschke s disease) which may simulate it but is a benign disorder ter minating in recovery (although lasting as long as a year) The onset is abrupt and usually follows an upper respiratory infection The disease is characterized by a diffu e nonpitting edema affecting the face neck, and upper part of the chest It differs from scleroderma in the rarity with which the hands and feet are involved Pleural effusion pericardial effusion, and hydrarthroses can also develop [969]

The cutaneous manifestations of scleredema adultorum are depicted in Figure 72 (Atlas page 45)

RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS

Relapsing febrile nodular nonsuppurative panniculitis (Weber Chris tian disease) is probably one of the more benign collagen disorders It should be remembered that in addition to the fever and subcutaneous nodules, typical lesions may also be found in the epicardial peripancreatic periadrenal, perirenal and me enteric fat ti sues—any of which could be responsible for atypical signs and symptoms [970 971]

The cutaneous manifestations of the Weber Christian disease are depicted in Figure 73 (Atlas page 46)

The cutaneous manifestations of polyarteritis are depicted in Figures 40 and 69 (Atlas pages 25 and 43)

If only for purposes of subsequent review by other interested clinicians, the records of patients with this disease should include a careful inquiry into their exposure to the sulfonamides, serum, hydantoins, iodides, thiouracil, mercurials, other drugs, and immunizing procedures In fact, several groups have attempted to define the entity of "hypersensitivity angiitis" as distinct both etiologically and pathologically from periarteritis [819, 949, 952] As previously noted, the symptoms of polyarteritis of the abdominal, polyneuritic, or polymyositic types may mask those of a secondary and concomitant acute porphyria hepatica (p 62) It has been suggested that the use of the Watson Schwartz test in these cases of arteritis might reveal a significant occurrence of the latter complication [22]

In regard to the kidney changes, there has been much discussion about the fanciful description of "telescopic urine' (a urine sediment consisting of red cell casts, albumin, double refractile oval fat bodies, and renal failure casts) *as being pathognomonic of visceral angiitis The author has noted* these urinary findings in classical chronic glomerulonephritis, this has also been the experience of others [950] It is very disturbing to observe the occasional development of the full picture of periarteritis (with uremia and subsequent death from this complication) in patients with chronic rheumatoid *arthritis who have received cortisone therapy* [17] Malignant hypertension has also been noted following the administration of cortisone in periarteritis [951] An acute generalized vasculitis with an extensive necrotic glomerulitis and a rapid uremia can complicate a malignancy elsewhere in the body [956a]

DERMATOMYOSITIS

Although dermatomyositis may begin with fever, malaise, Raynaud's phenomenon, various skin changes, serositis, and joint or central nervous system involvement, sooner or later the muscles become painful and exquisitely tender to pressure [953, 955] The muscles of the shoulder girdle, neck and arms are particularly susceptible There may be a marked dissociation between the subjective and objective muscular involvement in dermatomyositis, however [923c]

The cutaneous lesion often begins as a purplish discoloration of the eyelids It then progresses in the form of a heliotropic swelling of the circumorbital area and as a symmetrical violaceous erythema affecting the face, neck and trunk

The cutaneous manifestations of dermatomyositis are depicted in Figure 71 (Atlas page 45)

The histologic changes are not pathognomonic, even though practically all the muscles in the body (including the myocardium) are involved Several reports have recently appeared in which the association of this condition with malignant disease is stressed [956, 957] (It should be noted that a number of eminent pathologists have doubted the correctness of including dermatomyositis among the collagen disorders)

dyscollagenoses because of its striking clinical, serological, and pathological similarities to polyarteritis, lupus erythematosus (*vide supra*), and rheumatic fever

It is well to bear in mind that unexplained albuminuria in the patient with chronic rheumatoid arthritis may be a manifestation of secondary amyloidosis Reference has also been made under Group IV to the remarkable incidence of rheumatoid arthritis and other collagen disorders in agammaglobulinemia (p 146) The occurrence of an unexplained iritis in a young male should direct the clinician s attention to the possibility of an associated rheumatoid spondylitis A granulomatous pericarditis is not infrequently found at postmortem examination in patients with rheumatoid arthritis, most of these individuals are relatively free of spinal involvement

The error is frequently made of excluding rheumatoid arthritis in a middle-aged individual because of the concomitant presence of degenerative joint disease The poor mucin precipitate from the aspirated synovial fluid (with shreds and cloudy solution) a positive sheep-cell agglutination test and the characteristic changes in the synovial membrane can aid in this differentiation (pp 751 and 800)[973b] The drop latex fixation test appears to offer an even simpler, rapid and inexpensive method of diagnosing rheumatoid arthritis (p 751)

The diagnosis of *anarthritic rheumatoid arthritis* is obviously one that could be subject to much controversy, and should be made only when most other possibilities have been ruled out It has recently received some added support from the results of the differential sheep cell agglutination test[9 3] This variant is most apt to involve patients in the middle and latter decades Aside from the absence of frank joint involvement, it resembles the features of rheumatoid arthritis in most other respects In addition to the generalized aching of the muscles and limbs and such nonspecific manifestations as weight loss anorexia, other gastrointestinal disturbances, fever anemia, general malaise a markedly elevated sedimentation rate and headache, there may be rheumatoid nodules skin eruptions, and a lymphadenopathy

The correctness of grouping atrophic polyarthritis fever, anemia, neutropenia and splenomegaly under the designation of Felty s syndrome is still questionable The bone marrow findings are not specific and are actually those of chronic infection Amyloid di ease may have to be differentiated from portal hypertension in patients with long standing rheumatoid arthritis at the same time that the question of Felty s syndrome is raised

Similarly the failure of patients with either ankylosing spondylitis or psoriatic arthritis to yield positive reactions to the sheep-cell agglutination test and its various modifications (in contrast to the situation with Still s disease) would seem to argue against their being variants of rheumatoid arthritis (p 751)

"Steroid pseudorheumatism' is a definite clinical entity that is observed in patients receiving long term steroid therapy It can closely mimic rheumatoid arthritis[974] Since this complication is usually encountered when the latter disease is being treated, the rheumatoid patient may be-

RHEUMATIC FEVER

The cardinal features of rheumatic fever—the polyarthritis, pancarditis, chorea, subcutaneous nodules, and the dramatic response to salicylates—are too well known to merit any further discussion When these are atypical, however, and are associated with or clinically replaced by various skin eruptions (erythema marginatum or multiforme), fever, arthralgia, easy fatigability, anemia, purpura, abdominal pain, pleurisy, and epistaxis, prompt recognition is just as important This applies equally to children and adults Prompt diagnosis has become all the more imperative in view of the possibility of being able to prevent or minimize valvular and myocardial damage, both by the early institution of steroid therapy and subsequently by prophylactic antistreptococcal measures

Erythema multiforme and the nodules of rheumatic fever are depicted in Figures 8 and 21 (Atlas pages 7 and 13)

Even when it is quite advanced, *chorea minor* has been frequently overlooked by parents and physicians alike, being variously labeled as nervousness, tics, or muscular spasm habits The variability of the facial movements, the exaggeration of the choreiform movements after enforced quiet, speech dysfunction on counting, the "hung up" patellar reflex, and other clinical signs help in this differentiation The superimposition of an anxiety state onto recent rheumatic fever introduces serious difficulties in evaluating residual symptoms as evidences of activity

As the recent report of the special Committee on Standards and Criteria of the American Heart Association indicates, definite criteria are necessary in order to minimize both overdiagnosis and underdiagnosis[97] It is also stressed that beyond their diagnostic import, the subdivision of these manifestations into "major" and "minor" categories carries no significance either as to prognosis, amount of "rheumatic activity," or severity of the acute illness The combination of polyarthritis, fever, and elevated sedimentation rate is specifically cited as the *weakest* of all the various diagnostic combinations "Diseases to be ruled out include rheumatoid arthritis, gonococcal arthritis, lupus erythematosus disseminatus, subacute bacterial endocarditis, nonspecific pericarditis with effusion leukemia, sickle cell anemia, serum sickness (including manifestations of penicillin sensitivity), tuberculosis, poliomyelitis, undulant fever, and septicemias, particularly meningococcemia "

A number of unusual, but highly interesting and important clinical variations of rheumatic carditis were discussed in an earlier chapter because of the possibilities of their connoting a nonexistent bacterial endocarditis (p 114) These manifestations include petechial hemorrhages, retinal vessel embolism ' splinter hemorrhages" under the nails, hematuria splenomegaly, and hemoglobin pneumonia

RHEUMATOID DISEASE

Students of *rheumatoid arthritis* are all aware of the many diagnoses which are often made prior to the correct one, particularly in the case of the spondylitis[973] This disease is of unique interest to the students of the

dyscollagenoses, ochronosis, Reiter's syndrome erythema multiforme, serum sickness drug intoxications Raynaud s phenomenon sickle cell disease, acute leukemia, allergic vasculitis and purpura, periodic disease, and hypertrophic osteoarthropathy are individually discussed elsewhere in the text The appearance of a rheumatoid like syndrome in the first few months of life should direct attention to the possibility of the recently described entity of lipogranulomatosis (p 209)

Palindromic Rheumatism

Brief mention is made of palindromic rheumatism a condition characterized by abbreviated afebrile attacks of acute arthritis and periarthritis usually affecting only one joint The knees ankles, wrists and shoulders are the sites most commonly involved It is still uncertain as to whether this infrequent entity represents a variant of periodic disease rheumatoid arthritis, or an allergic state [978, 979]

ERYTHEMA NODOSUM

Among the rheumatic disorders one of considerable interest is that form of erythema nodosum which after careful study does not appear to be etiologically related to coccidioidomycosis tuberculosis lymphopathia venereum sarcoidosis chronic ulcerative colitis, or overt drug allergy (penicillin, iodides, bromides, sulfathiazole) It may be chronic recurrent and accompanied by fever hilar adenopathy, and albuminuria [980-982]

An illustration of erythema nodosum appears in Figure 5 (Atlas page 5)

Since the association of erythema nodosum with malignant disease is apparently very unusual one can justifiably conclude that bilateral hilar adenopathy is not likely to be due to malignancy if this eruption is also present [983] Another helpful clinical clue in this regard relates to the observation that while venous obstruction of the innominate vein or superior vena cava can occur in the lymphomas and other mediastinal malignancies, it is distinctly unusual in the benign forms of bilateral hilar adenopathy

CHRONIC POLYSEROSITIS

Mention should be made in this section of the group of variants under the entity commonly referred to as chronic polyserositis These differ primarily in the location of their predominant pathology *Pick's disease* describes the disorder in which there is a chronic adhesive or constrictive pericarditis It is associated with a chronic peritonitis involving the upper portion of the peritoneal membrane and the subcapsular area of the liver *Chronic hyperplastic perihepatitis* has also been described by the term *Zuckergussleber Concato s disease* refers to the same type of chronic proliferative serositis when it affects the great serous sacs *Jaundice is inconstant* and the liver function is usually well preserved until late The potential diagnostic difficulties in distinguishing these disorders from other causes of mediastino-pericarditis ascites hepatomegaly gastrointestinal

lieve he is experiencing an exacerbation Consequently, the physician might paradoxically continue to increase the dose of the steroid Since the availability of these hormones for clinical use, all clinicians dealing with rheumatic disorders have been commonly beset with the problem of evaluating patients in whom steroid therapy was instituted prior to the establishment of a definitive diagnosis of rheumatoid arthritis or nonarticular rheumatism

There are a few distinct features that could help to clarify the problem Whereas the predominant features of rheumatoid arthritis are referable to the synovitis and inflammation of the articular and periarticular tissues, the muscles and bones are the sites of predominant pain and tenderness in pseudorheumatism Emotional lability and memory deficits are also more characteristic of the latter, as is the aggravating effect of heat, exercise, and physical activity Gradual, but persistent, discontinuation of the steroid therapy must be pursued

"*Malignant rheumatoid disease*"—in which the valve rings, myocardium, kidneys, lungs, sclerae, and the serous membranes are involved in the granulomatous process—has been well described by Ragan and his associates[975] The pulmonary lesions can simulate acute atypical pneumonia, acute rheumatic pneumonia, or acute diffuse interstitial pulmonary fibrosis[975b] Unfortunately, massive hormonal therapy *is not* always effective here

The apparent relationship between *rheumatoid spondylitis and severe aortic insufficiency*—in the absence of any discernible history or evidence of rheumatic fever—has been recently presented in striking fashion[976] Pathologically, there is not only thickening and shortening of the aortic valves with fibrosis at the base (without commissural irregularity or obliteration), but also involvement of all layers of the aortic root, even with intimal calcification[976b] The gross resemblance to the aortitis of syphilis is apparent (i e , marked predilection for men, focal destruction of elastic tissue in the aortic ring leading to dilatation, scarring of the aortic cusps with retraction, rolling of the free margins, and focal calcification, clinical aortic regurgitation with rapid failure once decompensation occurs, and secondary coronary insufficiency)

Numerous serologic studies have been negative in these cases, including the *Treponema pallidum* immobilization tests Furthermore, the process rarely involves the aorta distal to its ascending portion A careful analysis of the tissues from these patients has failed to reveal the presence of Aschoff bodies Consequently the finding of new diastolic murmurs and defects in the A-V conduction in patients experiencing an exacerbation of rheumatoid spondylitis is most suggestive of rheumatoid aortitis A high incidence of both uveitis (58 per cent) and psoriasis (18 per cent) is also encountered

Atypical Arthritis in Systemic Illnesses

Reference has been made and will again be directed to the many systemic illnesses that are frequently first manifest by atypical multiple arthritis, more than a score are so listed in the American Rheumatism Association's classification[977] The joint involvement in gout, acromegaly, the

GROUP XI

Neoplastic Diseases

GENERAL CONSIDERATIONS

Variations in biologic behavior and span Spontaneous regression Statistical evaluations Variants of metastatic growth

DISORDERS IN WHICH THERE IS A PREDISPOSITION TO OR A HIGH ASSOCIATION WITH MALIGNANT LESIONS

Pernicious anemia Familial polyposis of the large bowel Chronic ulcerative colitis Familial adenomatosis Paget s disease of the bone Chronic lymphatic leukemia Undescended testicle Glucosuria and hyperglycemia Xeroderma pigmentosa Chronic arsenical intoxication Chronic draining sinus tracts Cirrhosis of the liver Hemochromatosis Irradiation therapy Syphilis (tongue cancer) Chronic stenosing jejunitis Chronic edema Chronic interstitial pulmonary fibrosis Polycystic disease of the liver The Maffucci syndrome The Peutz Jeghers syndrome Adenoma sebaceum

THE VARIANT MANIFESTATIONS OF CANCER

Fever Skin lesions (dermadromes) Herpes zoster Eosinophilia Elevated sedimentation rate Cryoglobulinemia Polyneuritis Effusions Steatorrhea Torulosis Adrenal insufficiency Diabetes insipidus Backache Hypercalcemia Hypoglycemia Hyperphosphatasemia Bowel and lung bleeding following anticoagulant therapy Myasthenia Anemia Polycythemia Cardiovascular complications Subacute cor pulmonale The superior vena caval syndrome General hypertrophic osteoarthropathy Cushing s syndrome

ELUSIVE PRIMARY MALIGNANT TUMORS

Krukenberg Tumors
Prostatic Carcinoma
Bronchogenic Carcinoma
Cancer of the Stomach
Malignant Melanoma
Carcinoma of the Pancreas

disease, tuberculosis, rheumatic fever, systemic lupus erythematosus, and the other collagen diseases are at once apparent [984]

OTHER DISORDERS OF CONNECTIVE TISSUE

Before leaving the subject of the collagen disorders, the so-called elastica disease, epidermolysis bullosa, and the Ehlers Danlos syndrome merit brief comment The basic derangement in all is an abnormality of elastic tissue, and *not* of collagen

The well documented association of pseudoxanthoma elasticum with angioid streaks and other retinal alterations (the Gronblad Strandberg syndrome), recurring phenomena of visceral, cerebral, and peripheral arterial disease, hypertension, and a hemorrhagic diathesis are described in *elastica disease* or "hereditary elastodystrophy "[986 988] An associated increased incidence of thyrotoxicosis, diabetes insipidus, Paget's disease of bone, and separation of the retina (most of these cases first come to the attention of the ophthalmologist) has been reported The skin lesions are bilaterally symmetrical and are usually noted in the neck and the flexural folds of the axillae, elbows, knees, and groin They appear as cream colored to orange papules (birthmarks) under the lines of the skin, and vary in size from a pinhead to a large pea The development of a yellowish lesion at the sites of trauma by a tight belt or corset has often given the initial clue to this diagnosis [987]

The cutaneous manifestations of pseudoxanthoma elasticum are depicted in Figure 74 (Atlas page 46)

Deficient elastic tissue is also encountered in *epidermolysis bullosa* wherein changes varying from occasional post traumatic bullae to severe cutaneous and mucous membrane lesions are observed (p 548) In the more severe types of this disease, known as acrodermatitis enteropathica, the fragile skin offers fertile ground for the growth of fungi These patients have even been reported as having generalized cutaneous mycoses As in the case of scleroderma, sarcoid, and adenoma sebaceum, there may be definite roentgenographic changes in the dystrophic type of epidermolysis bullosa These might include the following a claw like appearance of the hands, with acquired webbing and wedging of the distal phalanges, extensive caries and abnormally rapid attrition of the teeth, and a stenosing lesion of the esophagus at practically any level [98] This disorder will be discussed further in the chapter on Cutaneous Medicine (p 548)

The *Ehlers Danlos syndrome* is characterized in its fully developed state by cutaneous hyperlaxity, and by marked friability and fragility of the skin and blood vessels, with their subsequent splitting and the formation of hematomas and molluscous pseudotumors These may be noted subsequent to the slightest trauma Other associated abnormalities include large frontal bosses and prognathism Some instances of the Ehlers Danlos syndrome have not become manifest until the twenty to thirty year age group The orthopedist, the surgeon the roentgenologist, the pathologist, and the internist have all been puzzled by the various ' formes frustes" of this disease [989] (Also see page 547 under Cutaneous Medicine)

3 Patients who had cancer which was undiagnosed, despite a visible lesion of long duration

At the risk of repeating material that should be known to all physicians as a result of the promulgation of the so-called Seven Danger Signals of Cancer by the American Cancer Society (and of enhancing the problem of cancerophobia) the following seven potential diagnostic errors which may be made are deserving of further mention

1 The indiscriminate diagnosis of "canker sores in all mouth lesions without resort to biopsy of suspicious areas

2 The assumption of the benignity of a breast lesion under the diagnosis of mastitis or fat necrosis without resort to biopsy or surgical consultation

3 The prolonged conservative management of a gastric ulcer or of recent gastrointestinal complaints without initial or adequate follow up x ray examinations

4 The failure to appreciate the possibility that a prostatic or a bowel malignancy may be the basis of a long standing inguinal hernia suddenly becoming symptomatic

5 The prolonged treatment of uterine bleeding with hormones in the absence of a histologic diagnosis

6 The assumption that rectal bleeding stems from existing piles without recourse to proctosigmoidoscopic examination and barium enema

7 The prolonged therapy of primary" anemia without ruling out the possibility of either blood loss or a hemolytic process associated with a malignancy somewhere in the body

A listing and analysis of the many procedures which have proved valuable in the early diagnosis of neoplastic diseases may be found in Section X (Exfoliative Cytology) and in Section XI (Biopsies in Clinical Medicine) of Part II The term early" when applied to cancer diagnosis is often vague, since it may relate to clinical, histologic, anatomic, therapeutic prognostic, or biologic considerations

GENERAL CONSIDERATIONS

There is a growing appreciation of *the wide variation in the biologic behavior and pan* of the same cancer in different individuals, particularly after being influenced by modern therapy One should therefore never consider lightly a previously well documented diagnosis of malignancy when new symptoms develop, even after twenty to forty years have elapsed [992] The same applies to the previous diagnosis of a totipotential tumor For example, a localized follicle-type lymphoma may assume a generalized malignant transformation many years later [647] Students of cancer have found that recurrences following the five year period are sufficiently common to warrant abandonment of the term five year cure,' in favor of the more realistic expression five year survival without evidence of recurrent disease '[993]

The reader need hardly be reminded of the fact that cancer in infants and children accounts for about 10 per cent of the total deaths due to

Retroperitoneal Tumors

Idiopathic retroperitoneal and periureteric fibrosis

Nasopharyngeal Carcinoma

Esophageal Cancer

Carcinoma of the Right Colon

Primary Adenocarcinoma of the Appendix

Hypernephroma

Carcinoma of the Gallbladder

Neuroblastoma

CONSIDERATIONS IN THE DIAGNOSIS OF LUNG TUMORS

CONSIDERATIONS IN THE DIAGNOSIS OF MEDIASTINAL TUMORS

CONSIDERATIONS IN THE DIAGNOSIS OF LIVER TUMORS

BENIGN TUMORS INDUCING SYSTEMIC EFFECTS

Ovarian fibroma Myxoma of the heart Third ventricle tumors The endocrine adenomata Thymoma Echinococcal metastases Tumors at the ampulla of Vater, the cervical spinal cord, and the nasopharynx Endometriosis externa

PSEUDOMYXOMA PERITONEI AND PERITONEAL MESOTHELIOMA

BRONCHIAL ADENOMAS AND BRONCHIAL PAPILLOMATOSIS

CARCINOID TUMORS OF THE SMALL BOWEL

METASTASIZING "ADENOMA" OF THE THYROID GLAND

EVERY diagnostician worthy of this title must also automatically qualify as an expert in cancer diagnosis An interesting evidence of this fact can be found in Hunter's analysis of the diagnostic errors in the Cabot clinicopathologic conferences at the Massachusetts General Hospital over a twenty five year period [990] The vast preponderance of the mistaken diagnoses were in cases of malignancy In a comparable study of the antemortem diagnostic errors among 1106 autopsies performed at another institution, neoplasms ranked with infections as the most frequently missed diagnoses This was particularly striking in the case of brain tumors and hepatomas, the frequency of which were far out of proportion to their relative incidence among the total malignancies found [4b]

Generally speaking, it is true that the easier the diagnosis of a malignant disease, the poorer the prognosis In a review of the common errors relating to the diagnosis or management of cancer at one center, however, three major groups were defined by Laszlo and his colleagues [991] These included

1 Patients admitted with the diagnosis of advanced cancer in its terminal stage, but who had no cancer

2 Patients admitted with the diagnosis of advanced cancer in its terminal stage, but who had no evidence of local spread, and therefore were candidates for curative therapy

perthyroidism, and the presence of recent definite growth) On the other hand, the hysteria that has resulted in the wholesale thyroidectomies for asymptomatic multinodular goiters during recent years has yet to be completely justified

Detailed analyses of the incidence and sites of *metastases* in 1000 and 1303 autopsied cases of malignant neoplasms of epithelial origin, respectively, further emphasize the diverse patterns of tumor behavior [1002, 1003] The commonest sites include the abdominal nodes, liver lungs, mediastinal nodes pleura bone, adrenals, peritoneum and the serosal surfaces of the gastrointestinal tract The venous and lymphatic channels with their physiologically low pressures, are easily blocked this predisposes to bizarre patterns of intercommunication and often accounts for unusual sites of metastatic spread

The metastases of certain malignancies have the propensity for uniquely involving certain skeletal and soft tissue structures Two examples of this phenomenon are the "soap bubble" metastases to the sternum, skull ribs, and other bones from a renal cell carcinoma and the involvement of the phalanges of the hands and adrenal cortex by bronchogenic carcinoma [1004] Subsequent carcinomatous embolization to the lungs from metastatic liver disease has been described particularly in breast cancer [1005] Experience has shown that when hoarseness and recurrent laryngeal nerve paralysis are associated with a lung tumor, the neoplasm is usually primary in nature with surrounding involved nodes rather than being metastatic to the lung or mediastinum [1006a]

It should also be recalled that a small (or even microscopic) focus of malignancy can metastasize extensively Cancers of the testes and of the bowel occasionally behave in this manner A brain metastasis—histologically consistent with that of a bronchogenic carcinoma—is often discovered on exploratory craniotomy Even a retrospective review of the chest films may fail to demonstrate the primary lesion

DISORDERS IN WHICH THERE IS A PREDISPOSITION TO OR A HIGH ASSOCIATION WITH MALIGNANT LESIONS

One should also be aware of the several stigmata of various diseases and otherwise unimportant syndromes in which there is a high association with or a predisposition to malignant lesions In addition to those listed below, are adenoma sebaceum, polycystic disease of the liver, the Maffucci syndrome and the spotty melanin pigmentation or osteomatosis associated with polyposis of the small and large bowels These will be discussed further under Group XIV

1 The significant incidence of gastric cancer in patients with *pernicious anemia* who have been observed over sufficiently long periods of time is well known In one series of 1222 cases from the Boston City Hospital the rate approximated 10 per cent [1007]

2 The frequent occurrence of malignancy of the colon in *familial polyposis of the large bowel* and in *chronic ulcerative colitis* has been confirmed by many clinicians and surgeons [1008] In the latter disease the malignancies do *not* usually arise from the healed pseudopolyps

malignancy Every solid mass in this age group must be regarded as malig nant until excised and studied histologically [994]

Certain malignancies have shown a very definite change in clinical behavior over the past several decades This has been especially noteworthy in the case of primary cancer of the lung and liver Instead of the classic initial cough and pneumonitis due to involvement of the primary bronchi, we are now encountering the anaplastic "oat cell" lesion more commonly These tend to commence peripherally, spread centripedally, and present clinically with some manifestation of metastatic spread Similarly, a rise in the incidence of hepatomas and cholangiomas without an underlying cirrhosis has been noted over the past several decades [995a] This phenomenon is attributed to the increased number of patients with healed acute yellow atrophy, fatty nutritional cirrhosis, and exposure to toxins, as well as the general increase in longevity

As indicated above, survival may be quite prolonged, even in the presence of frank extensive metastases This is well exemplified by the large number of patients with thyroid adenocarcinoma who have survived fifteen and twenty years with only local cervical node spread—provided a compensatory rise in TSH is not induced by I^{131} or surgery (either biopsy or partial excision) [996, 998] There are many instances of patients with myeloma who have survived more than a decade after the diagnosis was initially made It has been estimated that there is at least an eleven times greater chance for the patient who has survived one cancer to develop another independent neoplasm

Although *spontaneous regression* of cancer is quite unusual, it has been well documented in isolated cases of malignancy involving the breast, the uterus, connective tissue, the stomach, and pigmented melanomas [999] It has occurred most commonly however, in neuroblastomas (particularly in children who have survived fourteen months after the diagnosis, even in the presence of extensive metastases) This phenomenon is probably a function of local tissue resistance during the periods of spontaneous arrest or regression that alternate with the periods of growth It may also be due to local inflammation, interference with blood supply, fever, and general metabolic or hormonal alterations The removal of a primary neoplasm is also observed to be followed by the regression of its metastases in a number of instances

Every physician should view all *statistical analyses* relating to cancer with a critical eye Nevertheless, he should also respect the reliable cumulative figures for the incidence and biologic behavior of certain tumors *commonly affecting the general population in an attempt* to formulate an intelligent prophylactic and therapeutic approach Nowhere is this consideration more important than in the appraisal of the relationship of "solitary" and multinodular thyroid disease to malignancy of this gland [1001] It has been well shown, for example, that the incidence of these nodules can vary in a given community from 8 per cent to 80 per cent depending on the geographical area Nevertheless, the annual number of deaths from thyroid cancer in the *entire* United States has been stationary at approximately 800 for several years One's attitude toward surgery must obviously be influenced by a number of clinical features (youth, "cold nodules," hy

10 Squamous cell carcinoma arising in *chronic draining sinus tracts* has been observed as a sequel to many types of chronic cutaneous sinuses and fistulas (osteomyelitic sinuses, fistulo-in ano, empyema sinuses, and war wounds)[1014]

11 While *cirrhosis of the liver* and *hemochromatosis* are frequently the underlying basis for the development of primary cancer of the liver, the relative rarity of metastatic carcinoma to the cirrhotic liver is noteworthy[1015b]

Postnecrotic cirrhosis, as well as Laennec s cirrhosis, is frequently complicated by primary hepatic carcinoma (occurring in 14 per cent of the 221 cases in one series)[317b]

12 With the longer periods of observation that have followed prolonged survival in patients who had been subjected to *intensive irradiation therapy*, it has become apparent that many tissues other than that of the skin are also prone to malignant degeneration Several such instances include the development of squamous cell carcinoma of the mucous membranes (particularly of the gastrointestinal tract) in the field of the treatment or adjacent to it,[1205] and the occurrence of osteogenic sarcoma of the skull as an aftermath to the irradiation of tumors in or on the skull[1 06]

The relationship to cancer of previous radiation in the form of the *radioisotopes* is significant It is generally conceded that (1) there is a decided increase in the incidence of leukemic degeneration in patients with polycythemia vera who have received P^{32} therapy (2) although the development of an acute leukemia in several patients who had received radioactive iodine within the previous two years is now considered coincidental,[663] future observations may change this point of view, (3) it may not be the radiation emitted by I^{131} which stimulates the growth of thyroid cancers, but rather the effect of the increased output of TSH resulting from the secondary hypothyroidi m[997] For this reason, Crile cautions that patients with inoperable thyroid malignancies should be treated initially with desiccated thyroid prior to being given radioiodine

13 Since a reactive serologic test for *syphilis* is found in close to one third of patients with *tongue cancer* one should not procrastinate in the seropositive patient who exhibits glossitis or leukoplakia by the administration of prolonged therapy for uncomplicated tertiary syphilis In fact, Castigliano concluded after a review of 2250 oral cancer patients who were treated at the American Oncologic Hospital in Philadelphia that the patient with evidences of tertiary syphilis in the oral cavity almost always has an associated cancer[553c]

The glossal manifestations of late syphilis are depicted in Figure 33 (Atlas page 21)

14 *Jejunal carcinomas* have been observed in patients with *chronic stenosing jejunitis*, suggesting a possible cause and effect relationship[170]

The necessity for a careful follow up of patients who have already been treated for one malignant tumor is further emphasized by the statistically proved observation that these individuals have a greater susceptibility to the development of other primary cancers The latter may originate either in the same system of organs—particularly with reference to the genital tract, the urinary tract, and the gastrointestinal tract—or elsewhere

3 The presence of *associated neoplastic abnormalities* in patients with *familial adenomatosis* has been attributed to their unusual mesenchymal tissue behavior In fact, they might alert the clinician to the existence of gastrointestinal polyps [1009a] These features include multiple exostoses, epidermoid cysts (sebocystomatosis), and fibromas, fibrosarcomas or leiomyomas, they are frequently found in subcutaneous, mesenteric, or retroperitoneal locations

4 An osteolytic sarcomatous degeneration of bone, usually composed of spindle cell fibroblasts rather than having the features of an osteogenic sarcoma, occurs in from 10 to 25 per cent of patients with *Paget s disease of bone* who reach their sixth or seventh decades [1010a]

In most instances, however, the annual restudy of patients with this disease by x-ray for osteogenic sarcoma is not justified The diagnosis is essentially a clinical one based on the development of pain or swelling, or both [1010b]

5 Moertel and Hagedorn found *leukemia or lymphoma* associated with a coexisting primary malignancy in their review of 194 cases from the literature and in 120 cases from the files of the Mayo Clinic [1011c] While there may be some question as to whether either of these hematologic disorders actually predisposes to the development of a specific malignancy, one should not be hesitant to diagnose an independent focal malignancy in patients with leukemia or lymphoma (especially of prolonged duration) if there is ample basis for such a diagnosis Several observers have pointed out the significant association of a concomitant carcinoma with *chronic lymphatic leukemia* [646, 1011]

6 The greater frequency of malignant degeneration in the *undescended testicle* has been established, although the significance of the statistical analyses still leaves much room for criticism [1012] While it does not appear necessary to excise all undescended testes as a measure of preventing neoplasia, Gross and Jewett are of the firm opinion that they should not be left in the abdomen or in the inguinal canal beyond the preadolescent years [101a]

7 While there is little doubt concerning the high incidence of *glucosuria* and *hyperglycemia* in association with *carcinoma of the pancreas*—probably due more to the interference with the escape of insulin from the pancreas than the actual destruction of the islets—there is still considerable controversy as to whether *diabetes mellitus* actually predisposes to the development of this neoplasm In a recent clinical and pathologic study of 609 necropsied patients with this tumor, however, Bell found the incidence *of pancreatic carcinoma to be three times greater in proportion* to the total cancer incidence in diabetics than in nondiabetic patients [1013]

8 The malignant changes in the skin which follow the radiodermatitis like atrophy, telangiectasia pigmentation, and verrucous keratosis of *xeroderma pigmentosum* are universally noted in these unfortunates

9 Similarly, the hyperkeratoses of the palms and soles resulting from *chronic arsenical intoxication* are subject to malignant degeneration

The cutaneous manifestations of arsenical intoxication are depicted in Figure 37 (Atlas page 23)

usually following several noncurative trials with the antibiotics [1019] It has become increasingly apparent that the *dyscollagenoses* (*especially dermatomyositis and scleroderma*) and certain malignancies are closely related clinically [956, 957, 967] This is evidenced by the occasional disappearance of the connective tissue reaction following resection or irradiation of the primary neoplasm The association of eruptions similar to *dermatitis herpetiformis* with various widespread malignancies also has been observed [1386]

An illustration of dermatitis herpetiformis appears in Figure 20 (Atlas page 12) Metastatic carcinoma to the skin is depicted in Figure 24 (Atlas page 15)

Kaposi s multiple idiopathic hemorrhagic sarcoma is an angiosarcoma that produces tender purplish nodules in the skin Their presence should suggest the possibility of other sarcomatous tumors in the gastrointestinal tract mesenteric lymph nodes, liver, lungs central nervous system, and bones [1385] There is probably a relationship between Kaposi s sarcoma and the lymphoblastomata [1413]

The cutaneous manifestations of Kaposi's sarcoma are depicted in Figure 23 (Atlas page 14)

An unexplained and marked *eosinophilia* may be one of the first indications of an obscure neoplasm, particularly in the presence of hepatic metastases [10 0] In such an instance it is usually a poor prognostic sign [10 1]

Markedly elevated sedimentation rates, *cryoglobulinemia* [807] *polyneuritis* [10 3] *subacute pleural and peritoneal effusions*, [10 4] *adrenal insufficiency*, [5b, 10 5] *steatorrhea* [158] *torulosis* [609, 611] and *diabetes insipidus* [106] are also occasional clues to malignant disease It is very common for the severe *backache* which later proves to be the presenting symptom of carcinoma of the pancreas or of a malignant infiltration involving the mesentery to be casually labeled as lumbago arthritis, or osteoporosis [1041]

The occurrence of *hypercalcemia* in generalized carcinomatosis with osseous metastases has on occasion closely simulated sarcoidosis myelomatosis, and the various metabolic bone disorders (particularly hyperparathyroidism) (p 82) [310, 31-] Large nonpancreatic tumors in either the thorax the abdomen, or the retroperitoneal areas at times present the feature of severe *hypoglycemia* (p 21) [60] This can be a rather striking manifestation with primary carcinoma of the liver [57] *Hyperphosphatasemia* (alkaline phosphatase) has been found to be a sensitive and early indicator of metastatic spread to the liver in the absence of icterus (p 87) [3 4]

An interesting clue to the diagnosis of a stomach or bowel malignancy may present itself in the form of gross *bleeding from the gastrointestinal tract following the institution of anticoagulant therapy* [10 68]

The occurrence of *hemoptysis during the course of anticoagulant therapy* poses even greater justification for the investigation of a possible occult bronchogenic carcinoma [1026b]

A *myasthenic syndrome* that might be confused with myasthenia gravis has been associated in a number of instances with certain malignant neoplasms particularly small cell carcinomas of the lung [10 2, 10 3] The relationship of thymomas and myasthenia gravis will be subsequently considered in Group XII (p 371) The weakness is often limited to the pelvic girdle and the thighs While marked sensitivity to test doses of curare occurs

in the body[1000] This sequence is most frequently encountered when a gynecologic tumor is the first of the multiple tumors Several observers have pointed out the apparent fact that those individuals who are subject to multiple primary tumors have slower growing neoplasms, possibly due to their greater resistance to tumor spread

THE VARIANT MANIFESTATIONS OF CANCER

Cancer can initially exhibit a number of very misleading symptoms and signs, of which some have already been mentioned, particularly in the discussion of the leukemias and lymphomas (p 181) Metastases need not necessarily be present

Fever of all descriptions may occur Retroperitoneal lymphoma and carcinoma of the kidney, in particular, often pose the problem of prolonged "fever of undetermined origin" (pp 105 and 184)[372, 665, 686] Consequently, pyelographic studies should be a routine part of the examination in all these patients It must be realized, however, that urography by any technique may show minimal changes since many renal tumors tend to expand laterally rather than medially Neither the presence of calcification nor multiple cysts positively excludes a renal carcinoma This is a consideration of added import when one recalls that papillary cystadenocarcinomas constitute a significant percentage of kidney neoplasms[1016]

Bluefarb has listed the following "Eleven P's" of the *dermadromes* encountered in the *leukemia lymphoma group and other internal cancers* which should promptly alert the physician to seek out an associated neoplasm[1017]

Pallor
Pruritus, including urticaria
Prurigo-like papules
Pyoderma
Pigmentations, including melanoderma and acanthosis nigricans
Pemphigoid or bullous lesions
Pityriasis rubra or exfoliative dermatitis
Posterior ganglionitis (herpes zoster)
Purpura, petechiae, and other vascular phenomena
Poikilodermatomyositis
Phlebitis

The reader is referred to Chapter XVII (Cutaneous Medicine) for a more detailed discussion of the cutaneous manifestations of neoplastic diseases (p 540)

The deeply pigmented, verrucous, papillomatous plaques of *acanthosis nigricans* associated with abdominal or thoracic malignancy usually develop in the intertriginous areas, the palms and the soles, the umbilicus, and occasionally on the nipples and mucosal surfaces[1018] It has been simulated by pseudoacanthosis nigricans, a condition that occurs in obese, darkly pigmented individuals and which abates following weight reduction

An illustration of acanthosis nigricans appears in Figure 1 (Atlas page 2)

An *inflammatory type of cutaneous metastatic carcinoma* can closely resemble cellulitis or erysipelas for weeks before its true nature is suspected—

The *cardiovascular manifestations* resulting from neoplastic diseases merit considerable emphasis The subject of symptomatic venous and arterial thromboses or emboli has already been discussed under Group VIII (p 211) The triad of endocarditis cerebral embolism with hemiplegia, and advanced cancer is also recalled (p 117) Either bacterial or aseptic thrombotic vegetations may be found on the heart valves in these instances [416, 417] The so-called *subacute cor pulmonale* due to a lymphangitic carcinomatous spread in the lungs—particularly from an unsuspected primary lesion in the breast stomach or even the lung itself—is not infrequently found at autopsy in a patient whose disease was misdiagnosed as "intractable status asthmaticus" [1030] When there is a fulminant and extensive lymphangitic invasion in patients who present with a lymphangitic carcinomatosis of the lungs, it is sometimes virtually impossible to ascertain definitely the site of the primary malignancy

Syncope and bradycardia may be the presenting symptoms of a bronchogenic carcinoma presumably due to the pressure exerted on the vagus nerves [1031] Hypertension is on occasion the initial clinical feature of a unilateral renal neoplasm with or without a tumor thrombus in the renal vein [10] The development of cardiac failure, cardiac arrhythmias or cardiac compression in patients known to have malignant disease suggests the possibility of metastases to the heart or pericardium [1033, 1034] In patients with advanced mammary carcinoma who are receiving large doses of estrogens, the appearance of considerable fluid retention may be related more to this form of therapy than to cardiac metastases [1181] The possibility of a radiation pericarditis should also be considered in patients who develop a friction rub and an enlarged cardiac shadow following high dosage radiation for a breast tumor or another malignant lesion of the chest (The author is currently caring for one individual with postmenopausal osteoporosis who repeatedly exhibits a weight gain of ten pounds within three days after ingesting two small estrogen tablets)

While the *superior vena caval syndrome* may be due to aortic aneurysms various inflammatory and infectious types of mediastinitis, and spontaneous thrombosis this manifestation should promptly arouse suspicion of a direct invasion of the venous wall by either a lung carcinoma a lymphoma or mediastinal metastases (*vide infra*) [1035, 1036]

An illustration of vena caval obstruction appears in Figure 45 (Atlas page 27)

A *generalized hypertrophic osteoarthropathy* occurs in many types of malignancy (renal carcinoma malignant seminoma, myelogenous leukemia carcinoma of the ovary esophagus epiglottis and larynx) and is of unique clinical importance [1037, 1038] Should this proliferative subperiosteal osteitis affect the distal ends of the extremities and their overlying periosteum in a slow manner, there may be little or no pain When associated with carcinoma of the lung or a pleural mesothelioma, this manifestation is of even greater significance since it may precede the spread of the tumor by a considerable period during which time curative surgery has already proved to be quite possible These patients are not infrequently first treated as having severe rheumatoid arthritis or acromegaly (It is well to recall the old adage that if narcotics are necessary to relieve pain ascribed

the response to neostigmine is poor. Electromyography and electric stimulation of nerves may aid considerably in this differentiation (p. 774).[1077]

Inasmuch as the finding of a cryptic *anemia* is frequently the first evidence of cancer, a brief discussion of this important subject is in order. Every clinician knows of many instances in which an unnecessarily protracted delay in the definitive diagnosis resulted from the institution of "shotgun" hematinic therapy prior to a concerted attempt to uncover the basis of an unexplained anemia. Reference has already been made to the significance of "dry taps" (p. 190), the presence of circulating immature granulocytes and of nucleated red blood cells in myelophthisic anemia (p. 203), hypersplenism (p. 193), and the great value of routine marrow studies for finding tumor cells in patients with obscure anemia or fever (p. 190).[689, 690]

It is significant to note that the hematologic manifestations of myelophthisis cannot be readily correlated with either the duration or extent of bony involvement, or the type of osseous metastases as judged by radiographic methods.[1067] Metastases from the lungs, breast, stomach, kidney, and thyroid are the ones most prone to induce such extensive bone marrow invasion. Attention has also been directed to both the increased incidence of gastric carcinoma in patients with pernicious anemia (p. 319), and the development of a megaloblastic anemia in patients surviving extensive gastrectomies and bowel surgery due to the resulting blind loops of bowel, intestinal strictures, or fistulae (p. 191).[700, 703, 1068]

A hypochromic anemia may result from the iron deficiency of protracted blood loss or following a gastrectomy. In addition, it can be due to an obscure diversion of iron in the "myelopathic" anemias of cancer. This often occurs even in the presence of a superabundance of total body iron.[1067] Along with the aforementioned progressive hypoferremia, Miller and his colleagues have presented clear evidence not only for the increased red blood cell destruction that takes place in patients with malignancy, but also for a "functional inadequacy" in erythropoiesis that exists in such an environment.[1070]

An acquired hemolytic anemia often assumes marked proportions in certain malignancies. This complication occurs most notably in chronic lymphatic leukemia, the lymphomas, ovarian teratomas, and to a much lesser degree in the carcinomatous diseases. It is felt by some observers that the neoplastic tissue itself serves as an antigenic stimulus to the formation of antibodies against the formed blood elements.[706, 1068] Such an immunologic process has been invoked to explain the presence of anemia, leukopenia, and thrombocytopenia when the marrow is hyperplastic and not diffusely invaded.[1069] (Other investigators still seriously question the evidence for this type of "autosensitization" or the presence of serologic agglutinins, however.) Finally, in the large number of cancerous patients whose anemia cannot be explained by the aforementioned mechanisms, the increased rate of red cell destruction appears to be due to a premature aging of normal erythrocytes in their circulations.[1067]

Polycythemia is infrequently associated with certain tumors. These include uterine fibromyomas, renal neoplasms, and cerebellar hemangioendotheliomas (p. 189).[685-687]

throughout the abdomen The scattered nodular opacities that represent these psammoma bodies within an ovarian tumor (benign or malignant) might easily be misconstrued as either fecal matter or the residuals of previously ingested barium or gallbladder dye The astute demonstration of such a finding in the area of a neoplasm affecting the bowel wall could justify the preoperative diagnosis of a Krukenberg tumor [1 00]

Prostatic Carcinoma

Reference was previously made to the fact that osseous metastases from a highly undifferentiated prostatic carcinoma may be osteolytic rather than osteoblastic (p 26) Such a tumor is occasionally unable to elaborate acid phosphatase, particularly following orchiectomy and estrogenic therapy [79b] Another of the fallabilities of the serum acid phosphatase determination is evident in the very high levels that might be encountered in patients with Gaucher s disease [283]

Bronchogenic Carcinoma

The numerous manners in which a bronchogenic carcinoma can become manifest are cited in many chapters of this book In addition to masquerading as almost *any* type of pulmonary pathologic condition, this very common neoplasm may present itself as a Horner's or Cushing s syndrome hoarseness,[1006] hyponatremia [305] osteoarthropathy, subacute cor pulmonale, polyneuritis, brain tumor adrenal insufficiency metastases to other organs (particularly the heart and kidneys), and the superior vena caval syndrome [461] A number of important considerations pertaining to the diagnosis of lung tumors will be cited later in this chapter (p 334) Where the possibility of a bronchogenic carcinoma is being entertained, one should view such occupational histories as ore mining chromate production asbestos manufacturing, gas work and nickel refining with greater interest

Cancer of the Stomach

The clinical lore relative to the immunity that a patient with a previous or active duodenal ulcer presumably possesses to the development of cancer of the stomach still persists in many quarters Certainly, the presence of an old ulcer scar in itself does *not* rule out cancer as the cause of a concomitant gastric lesion Furthermore, carcinoma has occurred in a significant number of stomachs after previous gastroenterostomy for duodenal ulcer, even involving the stoma in some instances [1046] It is not amiss to emphasize at this point that the initial manifestation of a gastric cancer may be that of a change in bowel habit (p 502)

Clinicians should be aware of the possibility that a carcinoma of the stomach particularly of the cardia, can be associated with a hiatal hernia [1046d] This relationship could represent either the development of the neoplasm in a pre-existing herniation or the hiatal development after the carcinoma as a result of the laxity of the hiatus and the local traction

to arthritis—and if gout is excluded—the patient probably has a more serious lesion, usually a malignancy)

It should also be noted that in addition to subacute bacterial endocarditis, the cyanotic types of congenital heart disease, pulmonary hemangiomas, and chronic pulmonary infections, generalized hypertrophic osteoarthropathy can occur in a number of extrathoracic conditions These include pyelonephritis, syphilis, alcoholism, chronic intoxication with phosphorus or arsenic, cholangitis, biliary cirrhosis (but rarely in portal cirrhosis), sprue, regional ileitis, and ulcerative colitis[1038] Another symptom complex to which clubbing of the fingers and toes can direct early attention is that of metaplasia of the urinary bladder mucosa with an associated mucous diarrhea[1038c] Unilateral clubbing of the fingers might prove to be a valuable early clue to the presence of a superior sulcus tumor, an arteriovenous aneurysm, and a subclavian or innominate artery aneurysm Great care must be taken, however, not to focus an undue amount of attention on familial clubbing, a benign condition that primarily affects males and begins in the teens

Clubbing of the fingers is depicted in Figure 34 (Atlas page 22)

ELUSIVE PRIMARY MALIGNANT TUMORS

In my own experience, cancer of the pancreas, the kidney, the retroperitoneal area, the lung, the stomach, the right colon, and melanomas have proved to be the most elusive malignant neoplasms This is particularly noteworthy and unfortunate in the case of the large bowel cancer complicating chronic ulcerative colitis[1009] Brief attention will now be directed to a number of these cryptic neoplasms Elusive liver malignancies and brain tumors are considered elsewhere (pp 344 and 363)

Krukenberg Tumors

The diagnostic evasiveness of the so-called Krukenberg tumors whether primary in the ovary or metastatic from the gastrointestinal tract, has been previously cited (p 35)[120] The subtle and relatively frequent *manner in which ovarian tumors that appear to be "primary"*—and are so removed at operations—subsequently prove to be metastatic lesions from the stomach or bowel is repeatedly emphasized by surgeons and gynecologists Instances are on record wherein an adenocarcinoma of a remaining ovary invaded the bowel many years after the other ovary had been removed for a benign cyst[1 0] In fact, some authorities even recommend that careful preoperative x ray investigation of the gastrointestinal tract and adequate preparation of the bowel for possible resection be routinely performed before undertaking surgery for pelvic tumors[1 0] It is stressed that age *per se* is not an important diagnostic factor when the possibility of an ovarian malignancy is raised in a young woman

The presence of numerous small calcifications seen by x ray within the area of an ovarian mass is characteristic of cystadenoma or cystadenocarcinoma, in the presence of metastases, they may become widespread

chapter to the statistically apparent increased susceptibility of patients with diabetes mellitus to the development of carcinoma of the pancreas (p 320)[1013]

When jaundice occurs due to involvement of the head of the pancreas this process may be suspected sooner The earliest differentiation between a carcinoma of the ampullary area and a carcinoma of the pancreas is vital inasmuch as there is a 25 per cent five year survival rate with the former but still practically none in the latter[1043 1044] Instead of waiting for widening of the duodenal loop and the inverted "figure-of 3 sign radiologists interested in this disease are now attempting to demonstrate the earlier changes in motor function and in the mucosal pattern of the duodenum and stomach

The finding of a dilated common duct can also be a significant and early secondary manifestation in this disease In view of this intimate relationship between the head of the pancreas and the common bile duct, intravenous cholangiography could prove to be of great value in the diag nosis of carcinoma involving the former organ[1041d] Since the liver becomes engorged with bile in the presence of complete and persistent extrahepatic obstruction—and is therefore usually palpable—the *absence* of hepatomeg aly may be a valuable clue in excluding obstructive jaundice due to a pancreatic tumor[3 1e]

In approximately one third of the cases the tumor affects the body or tail of the organ and there is no icterus There are several important clues which frequently can spell out this diagnosis to the alert clinician These include (1) persistent pain in either the abdomen or back (it may be localized or diffuse it is often associated with eating and aggravated by recumbency it is commonly relieved by sitting up or bending forward, due to the anatomical relationships of the pancreas) (2) a rapid, profound and unexplained weight loss (3) an unexplained change in the bowel habits (4) unexplained thrombophlebitis and (5) no significant anemia

Although the psychiatric manifestations of this neoplasm have received much attention they may well be provoked by the repeated indifference *of physicians to the patient s symptoms when the significant physical and* laboratory findings are at a minimum An abnormal glucose tolerance test and involvement of the left ureter or kidney shown by intravenous pyelog raphy has proved helpful in some instances (p 712) In addition to the occurrence of occult and repeated thrombophlebitis carcinoma of the pan creas may first become manifest by the features of a complicating bacterial or abacterial thrombotic endocarditis especially cerebral embolism and hemiplegia[417]

Significant gastrointestinal bleeding is encountered in approximately 15 per cent of patients with carcinoma of *any* portion of the pancreas[1041] This complication may result from infiltration of the alimentary tract either by the primary neoplasm or by its secondary deposits A number of case reports have shown that gastric and esophageal varices can ensue from the involvement of the portal system with or without hypersplen-ism[1045] An impairment of the blood coagulation mechanism might also con tribute to the bleeding diathesis in this disease

Malignant Melanoma

There may be marked variations in the clinical and histologic pattern of malignant melanoma, particularly when significant pigmentation is absent. This neoplasm has been known to mimic fibrosarcoma, epidermoid carcinoma, and malignant lymphoma.[1040a] Unless there is an unequivocal history of trauma to the eye for which the procedure was performed, the finding of an enucleated eye in the presence of probable extensive metastatic disease should immediately suggest the diagnosis of a *melanoma*. There are instances in which the interval between the eye operation and the evidences for metastatic spread was four to five years or longer.[1040b] The sites of the disseminated lesions may be very unusual in this cancer. They include not only the lung, the liver, and the peritoneum, but also the heart, the stomach, and the small bowel. A peculiarity of melanoma is its ability to metastasize to other tumors. Malignant melanoma may exhibit widespread and bizarre clinical and roentgenographic manifestations that involve not only the skin, but also the respiratory, skeletal, urologic, neurologic, and digestive systems of the body.[1040c]

It is very important to recognize and perform a biopsy upon a subungual melanoma (melanotic whitlow) as soon as possible because of the more favorable opportunity for cure when the melanoma occurs in this location. The early light brown discoloration in the nailfold, the eponychium, or the matrix can furrow or uplift the adjacent nail, but local ulceration does not occur until late. This lesion is frequently treated for months as a fungus infection, during which time extensive metastases may have taken place. The subject of melanoma will be further considered under Group XVII (p. 525).

Carcinoma of the Pancreas

One of the most elusive of all cancers in the body is carcinoma of the pancreas, an entity to which the author feels much emphasis should be directed in this type of treatise. It is all the more significant to the diagnostician since the prognosis in pancreatic cancer will continue to be hopeless in the majority of these cases unless the disease is constantly considered. Even in centers where clinicians are aware of this diagnosis, it is rarely made correctly ante mortem in more than 60 per cent of such patients.[1041]

The misdiagnoses are legion—and yet quite understandable—if one is not aware of this disease's natural history. They might include peptic ulcer, gastric cancer, duodenal obstruction, functional gastrointestinal syndromes, adynamic bowel activity with resulting fecal impaction, angina pectoris, arthritis of the lower dorsal spine, and pneumonitis or pleural effusion at the left lower lung field.[1042] It is also not unusual for the attending physician to be misled by a coincidental ulcer or gallstone. As previously noted, there is a striking predominance of male patients, mostly in their fifth and sixth decades; this span unfortunately overlaps the similar age-sex distribution in peptic ulcer. Reference was made earlier in this

colon (i e the cecum and the ascending colon) The importance of this truism is borne out by the potential surgical cure of these lesions even in the face of very large tumors or marked anemia This situation is obviously quite different from that which exists with comparable signs due to carcinoma of the left colon, inasmuch as the disease often remains completely limited to the bowel and the adjacent mesentery of the right colon for relatively prolonged periods The unfortunate fact remains however, that the current five year survival (less than 50 per cent) following resectional surgery, even by the best surgeons, for cancer of the right colon still does not exceed that of other large bowel tumors [1048d] In most instances, this is due to the long delay by physicians themselves in making the definitive diagnosis

It is highly instructive to review the causes for these diagnostic difficulties In a study of the experience at the Lahey Clinic with 80 patients who had carcinoma of the right colon Colcock noted that while abdominal pain was the commonest single symptom—being the initial complaint in 45 per cent of the cases —it was rarely constant or steadily progressive [1048d] In fact the discomfort was either intermittent or transient for weeks or even months He further points out the very important fact that in almost one half of these patients the initial manifestations were weakness fatigue, pallor and loss of weight while only nine patients (11 2 per cent) experienced any change in their bowel habit As a result, most of these patients are treated for a presumed 'primary anemia diverticulitis peptic ulcer gallbladder disease, "chronic appendicitis, or heart disease over a period of months before any serious re evaluation of the diagnosis is forthcoming The presence of seven physician patients in the above cited group should also be very sobering to diagnosticians

Mucus producing carcinomas of the cecum tend to be more malignant and to occur with greater frequency in the younger age groups The many manners in which this tumor might present itself are demonstrated by one recent clinicopathologic report concerning a young woman who exhibited fever weight loss hypoproteinemia biliary obstruction with jaundice and marked hypercholesterolemia due to (1) the compression of the hepatic duct by metastases to the hilus of the liver and (2) metastases to the ovaries with the picture of a Krukenberg tumor [1048]

Surgeons should examine the large bowel for a possible malignancy if a patient over the age of thirty years undergoes a laparotomy for a suspected appendicitis, and the appendix is found to be normal [1343] About 2 per cent of patients with large bowel carcinoma are less than thirty years of age

Another unfortunate factor that often causes the clinician to miss the diagnosis of carcinoma of the cecum pertains to the errors in radiographic interpretation which are apt to be made Every experienced radiologist is keenly conscious of the elusiveness of right colon carcinomas and harbors particular respect for lesions of the cecum seen by x ray Once the diagnosis is finally established the history is not infrequently obtained of a suspicious area noted on a previous barium enema but not studied again

When the anatomical relationships between the transverse colon and the stomach are considered it is not surprising that both the symptoms

Retroperitoneal Tumors

The elusive nature of retroperitoneal tumors (particularly lymphomas) was discussed in an earlier chapter (p 184)

In the differential diagnosis of pancreatic cancer, brief mention is made of the entity known as idiopathic retroperitoneal and periureteric fibrosis, of which about a dozen cases are on record In several of these patients, reoperation was performed because of the possibility that an underlying retroperitoneal or pancreatic tumor had been overlooked This can be readily appreciated when one considers the profound weight loss encountered, along with the severe pain in the back that is aggravated by lying flat [667, 668]

Nasopharyngeal Carcinoma

Another malignancy that merits some discussion because it is infrequently considered—even in the presence of frank cervical node metastases—is the nasopharyngeal carcinoma It has been noted that without the use of the nasopharyngoscope, the nasopharynx is the most frequent blind spot in the diagnosis of all tumors of the aerodigestive tract [1047] The majority of these patients are first seen because of a cervical adenopathy The reference of symptoms solely to the ear (unilateral deafness or tinnitus) is a frequent occurrence in this disease Similarly, an invasion through the foramen lacerum may result in an external rectus paralysis or diplopia, which in turn will direct the patient to an ophthalmologist One unique feature of nasopharyngeal tumors is the distinct racial susceptibility of orientals, especially the Chinese Widespread metastases with leukemoid responses may result from these small and highly anaplastic epidermoid carcinomas and lymphosarcomas The justification for such designations as lymphoepithelioma and the "Schmincke tumor" is still disputed

Esophageal Cancer

Palpable lymph nodes occur in only 5 per cent of patients with esophageal cancer In the unusual case characterized by the absence of dysphagia, this disease might initially present itself as a mediastinitis, an aortic perforation with exsanguination, or as a tracheoesophageal or bronchoesophageal fistula Similarly, gastrointestinal hemorrhage, cough due to the invasion of either the trachea or the left main bronchus, dyspnea, and hoarseness secondary to a paralysis of the recurrent laryngeal nerve are occasional presenting features of an esophageal carcinoma [1249c] In addition to dysphagia, the symptom of burning after the swallowing of hot liquids may be an early sign of esophageal cancer An attempt should be made to differentiate esophageal squamous cell carcinomas (which almost never invade the stomach) from adenocarcinomas of the cardia (which frequently extend to the esophagus)

Carcinoma of the Right and Transverse Colon

Another malignant neoplasm that frequently merits a high index of suspicion in the presence of unexplained illness is *carcinoma of the right*

have been added) clearly serves to point out the numerous guises under which this neoplasm can assert itself to the clinician

ANALYSIS OF DIAGNOSTIC DIFFICULTIES IN HYPERNEPHROMA

	Number	Per cent
Fever of undetermined origin[372]	7	2 5
Secondary amyloidosis (proteinuria azotemia hepatosplenomegaly)[201]	8	3 0
Signs of debility as the sole manifestation (weight loss anorexia anemia weakness)	5	1 8
Polycythemia[686]	5	1 8
Misdiagnosed abdominal mass	10	3 6
Presenting complaint—pulmonary	10	3 6
Presenting complaint—osseous	8	3 0
Presenting complaint—neurologic	5	1 8
Metasta is 14 years following a nephrectomy	1	0 4
Absence of hematuria	120	44 0

Patients with renal cell carcinoma may exhibit not only polycythemia but also a profound leukemoid reaction characterized by mature leukocytes and the absence of splenomegaly[1049] (An erythrocytosis can be associated with a benign renal lesion—not necessarily a tumor, but even a hydronephrosis—the removal of which has induced a prolonged remission)[686] The prolonged duration of the hematuria and other features of certain transitional cell papillary carcinomas which involve the renal pelvis is occasionally quite striking[1049b] In spite of their apparent histologic benignity, it is always wise to regard these neoplasms as malignant

CARCINOMA OF THE GALLBLADDER

Since an associated carcinoma of the gallbladder might not be suspected by the surgeon who is performing a cholecystostomy particularly in the aged, it is wise to submit a portion of this organ for pathologic study under these circumstances[1048b] The significance of this maneuver is emphasized by the fact that in 85 per cent of the patients with carcinoma of the gallbladder who do not present themselves primarily with evidence of liver metastases the carcinoma is clinically indistinguishable from benign disorders affecting the biliary tract

In a review of 33 cases from the Massachusetts General Hospital,[1048b] contrast studies of the gallbladder merely revealed stones or nonfunction of this organ in 12 cases while the upper gastrointestinal studies furnished valuable information from the deformity of the stomach or duodenum caused by the gallbladder tumor in 18 instances

NEUROBLASTOMA

Cognizance must be taken of the fact that *next to leukemia neuroblastoma* probably represents the most common malignant tumor encountered in infancy and in childhood Accordingly this diagnosis should be

and the radiographic appearance resulting from the extension of a carcinoma of the transverse colon might be misconstrued as representing a primary gastric malignancy [1049f, g] (The distal three fifths of the transverse colon is situated immediately below and slightly posterior to the greater curvature of the stomach—these two organs being connected by the short segment of the greater omentum known as the gastrocolic ligament) In such an individual who exhibits various defects on the greater curvature, with or without ulceration or fistula formation a barium enema must be given The importance of this approach is pointed out by the fact that a number of these colon carcinomas have not yet metastasized to either the lymph nodes or the liver, and accordingly offer a much greater chance of surgical cure than could be anticipated with gastric carcinomas

Three additional roentgenologic considerations should be set forth in this regard (1) the fistulous tract may be unidirectional, or the fistula may be patent only intermittently (2) intramural neoplasms of the stomach (most notably leiomyomas and leiomyosarcomas) may closely simulate the picture of a gastric extension from a carcinoma of the colon, and (3) it may be impossible to define the primary site of the tumor in certain instances in which case the bowel must be adequately prepared preoperatively *It is also highly important for the radiologist to search diligently* for an underlying tumor when obstruction is present in either the transverse or the ascending colon, notwithstanding the presence of diverticula in these or the adjacent areas [136 e]

The frequency with which clinicians surgeons, and gynecologists are repeatedly misled into diagnosing a primary tumor of the bowel in patients with ovarian carcinoma—and vice versa—was pointed out previously (p 326) [1 0]

Primary Adenocarcinoma of the Appendix

Since more than one half of the reported cases of primary adenocarcinoma of the appendix have presented with symptoms suggesting acute appendicitis and since this diagnosis is usually not suspected even by the surgeon at the time of operation, careful histologic study of *all* removed appendices must be insisted upon [1048a] Notwithstanding the general impression to the contrary this rather uncommon neoplasm can produce widespread metastases, including a linitis plastica type of lesion in the colon Only prompt diagnosis, aided by frozen section study will obviate a dangerous delay in proper resection and prevent needless secondary operative procedures

Hypernephroma

Numerous references to the systemic manifestations of hypernephroma appear throughout this book In the absence of hematuria flank pain or a palpable mass in the flank, these patients will obviously not seek urological consultation The following analysis of the diagnostic difficulties encountered in a review of 273 cases of proved hypernephroma from the Mt Sinai Hospital in New York [1049a] (to which several of these references

it is well to be cognizant of the fact that carcinoma of the lung can also supervene

The finding of histologically normal prescalene and deep cervical lymph nodes obtained by biopsy of the cervical fat pads makes benignity of one or several masses in the lung more likely See Section XI of Part II (p 798) Similarly, the finding of nodes that are diagnostic for metastatic carcinoma, lymphoma, sarcoidosis, tuberculosis and other types of pathologic conditions can help to obviate both a diagnostic thoracotomy and an unnecessary pulmonary resection

Reference is also made to nocardiosis (p 169)[615] pulmonary infarction (p 129)[454] localized bronchiectasis[105] lipoid pneumonia (paraffinoma) (p 127)[447] a dilated azygos or hemiazygos vein (p 236)[83 105d] the right middle lobe syndrome (p 151),[539] radiation pleuropneumonitis (p 398),[1198 1199] enlarged lymph nodes (p 301),[916b] mucoid impaction of the bronchi (p 128),[449] retropleural hematoma following sympathectomy (p 457)[1 79b] and the so-called "vanishing lung tumor" due to a localized interlobar effusion in unrecognized congestive heart failure (p 129)[83 e] Each of these pathologic states has caught the most expert of diagnosticians off guard by its ability occasionally to simulate pulmonary neoplasia For example the lipoid in an oil aspiration pneumonitis can assume widespread or localized distributions—especially in the right lower lobe and the right middle lobe—depending on the position and activity of the patient[447e]

While the protrusion of an *accessory lobe of the liver* into the diaphragm is usually infradiaphragmatic, instances of true intrathoracic accessory lobes are on record[1058b] The possibility of a diaphragmatic liver herniation following trauma should be considered in the differential diagnosis of pulmonary pleural or diaphragmatic tumors when the nature of the mass is not evident and when the density is inseparable from the diaphragm Pneumoperitoneum can be of diagnostic value in such a situation[1058c]

Twelve instances of nontraumatic (and presumed congenital) *superior ectopy of the kidneys* have been reviewed by Berlin, Stein and Poppel[105] The performance of pyelography may accordingly establish the diagnosis of renal ectopy in the presence of an undiagnosed lobular mass at the posterior lung base

The common problem of *delayed resolution of pneumonia* and the approach to this potentially neoplastic process has been discussed under Group IV (p 120)[4 3 4 4] The wide variety of pulmonary malignancies that can present as lung cavities was also considered there[465] The ability of a bronchogenic carcinoma to masquerade as a thin walled cyst is again emphasized[1006b]

The roentgenologic demonstration of *calcification within a solitary pulmonary mass* as it relates to the benignity of the lesion deserves some comment It is becoming increasingly apparent that a solitary circumscribed nodular lesion of the lung can only be regarded as benign from the roentgenologic viewpoint if there is clear evidence of a laminated or "popcorn type" calcification It has been repeatedly shown however that calcification is at times found in the center of a carcinoma This may be due either to the deposition of calcium in its necrotic portions or to the

entertained when a mass is noted in either the abdomen or in the paravertebral region, particularly if the tumor is in the adrenal area and contains calcium (Calcification is actually encountered only rarely in cases of Wilms' tumor) Approximately one half of the 32 patients with proved neuroblastoma reported from the Mayo Clinic had skeletal metastases by the time of admission The radiographic appearance of the metastases is often distinctive in the following aspects (1) there is a tendency to a bilaterally symmetrical distribution of the lesions, (2) there is a predominance of mixed destructive and proliferative bone changes, (3) cortical destruction and a "sunburst type" of periosteal reaction frequently occur, (4) the tumor occasionally extends into the soft tissues, and (5) pathologic fractures may take place [1039]

CONSIDERATIONS IN THE DIAGNOSIS OF LUNG TUMORS

It must be appreciated that in certain patients in whom there is reasonable evidence that a primary malignancy has been controlled, the presence of another *discrete lesion in the lung* may be indication for excision, rather than a contraindication against it In good hands, the risk of an exploratory thoracotomy has decreased to the point where it is frequently not wise to adopt a wait and see attitude in managing certain indeterminate intrathoracic lesions This positive approach is necessitated on occasion by virtue of the increased statistical possibility that the mass might represent a second and completely independent primary pulmonary malignancy [1050] For example, in one postmortem study of patients in whom a squamous cell carcinoma of one lung had been previously resected, microscopic carcinoma *in situ* was found in the "good" lung in five cases [1050c]

It has become apparent to clinicians, radiologists, and thoracic surgeons that carcinoma of the lung in reality grows more slowly and over a longer period of time than was suspected several years ago, especially when the malignancy arises peripherally In this regard, Rigler believes that more than one half of these patients in retrospect show x ray evidence of their disease more than two years prior to either the appearance of symptoms or the making of a definitive diagnosis [1050d]

An aggressive surgical attitude is further justified by the fact that a host of benign tumors and other disorders can present themselves in the form of localized or rounded intrapulmonary densities In one series of 20 patients with presumed pulmonary metastases in whom such a surgical approach was adopted, four independent tumors were found, of which three proved to be benign [1051a] In another series of 215 cases of solitary pulmonary nodules encountered in the Washington, D C area, there were 82 radiographically noncalcified granulomas found [1051b] Study by special stains revealed the following positive diagnoses tuberculoma 17 per cent, histoplasmoma 55 per cent (*note*), and coccidioma 7 per cent Chronic localized pulmonary brucellosis due to *Brucella suis* may result in a caseous granuloma that is indistinguishable histologically and roentgenographically from that due to tuberculosis [433b] Even when one is dealing with individuals who have proved pulmonary tuberculosis [535b] coccidioidomycosis,[435] or asbestosis[444b c]—in which the radiographic appearance might be misleading—

Analysis of 141 Cases of Mediastinal Tumors

Group A (primary mediastinal tumors)	Number of Cases	Number Malignant
Lymphoma	29	29
Neurogenic tumor	25	1
Bronchogenic cyst	13	0
Teratodermoid	12	2
Pericardial cyst	9	0
Sarcoid	7	0
Thyroid enlargement	5	0
Granuloma	5	0
Thymoma	5	2
Angioma	3	0
Primary carcinoma	3	3
Sarcoma	2	2
Fibroma	2	0
Lipoma	2	0
Liposarcoma	1	1
Chylous cyst	1	0
Leiomyoma	1	0
	125	40

Group B (other mediastinal tumors of neoplastic non neoplastic and vascular origin)	Number of Cases	Number Malignant
Vascular lesion		
Aneurysm		
Cardiac	3	0
Aorta	2	0
Pulmonary artery	1	0
Carotid artery	1	0
Other		
Right-sided aorta	1	0
Coarctation of the aorta	1	0
Bronchogenic carcinoma	3	3
Metastatic carcinoma	3	3
Azygos lobe	1	0
	16	6

with a problem in delicate vascular surgery with which he is unable to cope after the chest has been opened Body section radiography may be of limited value in defining the nature of a mediastinal tumor (p 802) The chief drawback to the use of kymography in distinguishing between solid tumors and aneurysms is posed by the frequent presence of a laminated clot within the latter structures which precludes the visualization of wide pulsations [903] A diagnostic pneumothorax or pneumoperitoneum may help to differentiate certain tumefactions of the diaphragm and the lung The use of diagnostic pneumoperitoneum has proved of particular value in the diagnosis of tumors or simulated tumors situated at the right cardiophrenic angle The diagnostic value of a pneumothorax is considerably limited by the presence of adhesions however

On the whole most chest specialists currently regard the practice of diagnostic x radiation to the mediastinum as unwise except in certain

neoplasm engulfing a pre existing calcified focus [1059] In an analysis of the pathologic specimens from 207 such cases of discrete pulmonary nodules studied at the Mayo Clinic, calcification could be demonstrated by x ray in 13 9 per cent of the malignant lesions [1059c]

CONSIDERATIONS IN THE DIAGNOSIS OF MEDIASTINAL TUMORS

Clinicians who deal in large measure with diseases of the chest are both impressed and somewhat awed at the striking shift in emphasis that has taken place over the past decade in the approach to the diagnosis and management of mediastinal enlargements Whereas watchful waiting and diagnostic radiation were the frequent keynotes only a few years ago, a large number of these patients are currently being subjected to diagnostic *thoracotomy in many centers While it is true that most mediastinal* lesions require this surgical approach for ultimate diagnosis, many of these operations might be obviated if certain valuable diagnostic procedures are carried out (*vide infra*)

A number of excellent reviews have appeared in recent years dealing with the panoramic subject of mediastinal tumors and with reviews of the various individual causes for such enlargements [1053] The analysis of 141 cases studied by Nelson Shefts, and Bowers—*representing* the extensive accumulated experience at several large diagnostic centers and in a private thoracic surgeon's practice—is noteworthy [1053a] A good perspective of the entire subject can be achieved by listing the entities in their proportional order of incidence as encountered by these thoracic surgeons (The diagnosis was proved by surgery, autopsy, or angiocardiography in every case) (See table on page 337)

As will be evident when the individual entities are discussed, there is a wide variation in the location within the mediastinum which any given tumor may occupy In fact, it is virtually impossible *to set forth* any rule of thumb to which many exceptions have not already occurred In general, tumors of neurogenic origin esophageal tumors and gastroenteric cysts tend to locate *within the posterior mediastinum* lymphoid neoplasms bronchogenic cysts and pericardial cysts usually occupy the *middle mediastinum*, while intrathoracic goiters tumors of the thymus and teratomas occur most commonly in the *anterior mediastinum*

With reference to symptoms, benign tumors as a rule produce few complaints unless the growths reach very large proportions Pleural effusions, superior vena caval obstruction (p 325) thoracic duct obstruction irritation or paralysis of the phrenic *recurrent* laryngeal and other nerves, *and a peripheral lymphadenopathy are most often indicative of* malignancy Patients with root pain due to a mediastinal tumor may present themselves because of suspected angina pectoris

With reference to diagnostic aids, much emphasis should be placed on the following (1) scalene lymph node biopsy *(p 798) for the diagnosis of* lymphomatous diseases, a number of the infectious and noninfectious granulomatous diseases, and malignancies of both pulmonary and mediastinal origin and (2) angiocardiography *for the diagnosis of vascular lesions within the mediastinum* (p 783) [916] If the latter study is not utilized in the diagnosis of mediastinal enlargements, the surgeon may be confronted

There are four features of *teratodermoids* within the mediastinum which merit some comment.[1054] First, calcium deposits are almost always present, even though the finding of mature bone or tooth formation is rather unusual. Second, patients with these tumors often experience symptoms referable to the chest (pain, cough, dyspnea, substernal fullness) that lead them to consult their physicians. The atelectasis and pleural effusion resulting from the reaction incited in the adjacent tissues by a large teratodermoid tumor may produce the appearance of a mass lesion or effusion affecting an entire hemithorax. Inasmuch as most of these tumors are presumed to be present at birth, their high incidence in mediastinal tumors among infants and children (14 out of 45 tumors in one series) is not surprising.[1053e] Third, these tumors are most often located in the anterior mediastinum. On rare occasions, however, dermoid tumors of the mediastinum might assume a posterior location.[1053d] Finally, enlargement of the tumor may occur gradually (over a period of weeks) when there is a malignant change—as occurs in approximately 15 per cent of these tumors—or suddenly when there is either hemorrhage or infection within the tumor, or where radiation therapy is being delivered to a malignant teratoma.

Pericardial cysts are virtually uniformly asymptomatic and most often come to the clinician's attention following a routine chest film. The great majority of these cysts present themselves at the right anterior cardiophrenic angle. A demonstrable communication with the pericardium is unusual, as is the presence of malignancy or other complications.[1054d]

The subject of *sarcoidosis* is considered in detail under Group VII (p. 204). This disorder must always be considered in the evaluation of mediastinal enlargements. While the diagnosis is readily made in the presence of both the pulmonary infiltrations and the typical bilateral hilar adenopathy, it may be difficult to come by if only the mediastinal nodes are enlarged (especially when on but one side), and as spontaneous remissions and exacerbations occur. There are several potential hazards to a trial diagnostic course of radiation therapy should an erroneous tentative diagnosis of lymphoma be made in a patient with sarcoidosis. Here—possibly more so than in any other condition—the results of the scalene node biopsy technique are apt to be frequently rewarding.

The high incidence of goiter in itself makes it mandatory to consider the diagnosis of an *intrathoracic (or substernal) thyroid enlargement* when confronted with a mediastinal tumor, particularly if it is found within the superior segment. While the descension of the thyroid occurs anterior to the trachea and the esophagus in most cases, there are about 40 instances of posterior intrathoracic goiter on record.[1054] The difficulty in distinguishing bronchogenic cysts from these tumors was commented upon earlier. Fortunately, the diagnosis of a thyroid tumor can usually be made if the following four criteria are kept in mind: (1) the presence of a mass in the neck, (2) the movement of the mass on swallowing, (3) the appearance of the tumor in the superior mediastinum by x-ray, and (4) the uptake of radioactive iodine by the tumor.[1053] Although the last study may prove to be diagnostic, the clinician is reminded that a thyroid mass might not take up the isotope if there is no functioning thyroid tissue present. This was exemplified by one recent case report in which a mediastinal nontoxic

very limited circumstances (p 814) A 25 per cent decrease in the size of a mediastinal lymphadenopathy in response to small amounts of radiation is suggestive of a radiosensitive reticuloendothelial tumor, most notably Hodgkin's disease Unfortunately, not only may the results so produced be misleading, but prolonged roentgen therapy can render the subsequent surgical removal of a benign tumor very difficult

Several pertinent comments bearing upon the diagnosis of a number of the conditions that give rise to unexplained mediastinal enlargement will now be set forth Their relative frequency—as listed above—will serve as the basic frame of reference

Hodgkin's disease, lymphosarcoma, and reticulum cell sarcoma constitute the majority of the *lymphomas* encountered within the mediastinum It is emphasized that involvement of neither the cervical lymph nodes nor other structures need be present, and that unilateral enlargement of the mediastinum does *not* exclude the presence of a lymphoma [1054a] Even when palpable cervical lymph nodes cannot be felt, the results of a scalene node biopsy (best performed on the side with the greatest involvement) may prove to be fruitful These neoplasms are not infrequently first uncovered by routine chest films in patients who are either asymptomatic or who have such vague constitutional symptoms as a low grade fever, fatigue, and unexplained weight loss (p 181)

The *neurogenic tumors* usually encountered in the mediastinum consist of neurofibromas, ganglioneuromas, and neurilemmomas The majority of these neoplasms are located within the posterior mediastinum and appear as rounded tumors of even density with distinct borders Occasionally, they are found as asymptomatic densities either in the superior mediastinum or in the middle mediastinum, and accordingly may be confused with bronchogenic cysts and thyroid tumors A Horner's syndrome could result from involvement of the cervical sympathetic nerves Bone erosion (in contradistinction to bone destruction) is commonly associated with neurogenic tumors On the other hand signs of cord compression due to an underlying mediastinal tumor of neurogenic origin are encountered only rarely Radiographically demonstrable calcification may be noted in cases of ganglioneuroma [1053d]

Bronchogenic cysts represent a sizable proportion of the mediastinal tumors in most of the reported series Since these structures probably originate as embryonic derivations from the budding foregut, they can be situated at any site along the tracheobronchial tree or the esophagus In view of their many possible locations in the mediastinum and the absence of any specific diagnostic criteria by x ray, the correct diagnosis is rarely made prior to surgery Even in the hands of the pathologist the definitive nature of these cysts has proved elusive since the pressure exerted by the contained fluid may obliterate the lining epithelium Nelson Shefts, and Bowers encountered three instances in which it was impossible preoperatively to distinguish a bronchogenic cyst from either a cervical or substernal thyroid enlargement [1053a] As is also the case with other benign mediastinal cysts, obstructive symptoms can suddenly develop when hemorrhage or infection takes place within a bronchogenic cyst A pericardial defect might also be encountered with this type of cyst [1054b]

cavernous hemangioma, a hemangioendothelioma or a cavernous lymphangioma [105a, 105b, c, d] It has been the general experience that while they appear benign histologically these tumors are frequently locally invasive Accordingly, it may be impossible to excise them completely

The diagnosis of a *primary mediastinal carcinoma or sarcoma* always incites considerable discussion and controversy This diagnosis is probably justified in those unusual instances where no primary malignancy can be found either in the lung or elsewhere in the body [1056a, b] These malignancies might originate from the thymus, a teratoma or some other form of an embryonic rest The presenting features of this tumor are usually dyspnea pain in the chest, hoarseness, and evidence of a relentless obstruction of the superior vena cava

Thirteen patients exhibiting mediastinal masses which resembled thymomas both grossly and microscopically were shown actually to have had a peculiar form of *lymph node hyperplasia* These nodes were histologically characterized by germinal center formation and marked capillary proliferation [1056]

Intrathoracic lymph node enlargement is occasionally encountered in asymptomatic individuals *as a transient benign condition* completely unassociated with either a preceding illness or evidence of involvement of other viscera [1056d]

Gastroenteric cysts are most commonly found in the posterior mediastinum close to the pulmonary hilus from which site extension into either chest cavity is possible [105, b] These cysts may be lined with primitive esophageal epithelium gastric mucosa intestinal mucosa or with a mixed epithelium that is representative of both the respiratory and intestinal tracts (This histologic peculiarity stems from the embryologic observation that for several weeks during its normal development the esophagus contains many epithelial lined cysts within its wall with a multi potential epithelium that can produce ciliated squamous or mucous cells as well as a gastric mucosa) Olken has pointed out that three fourths of these cysts make their symptomatic appearance within the first year of life [1057] When encountered in adults they usually lie in the lower half of the esophagus between the muscle layers of the esophageal wall There is rarely a persistent communication with the lumen of the esophagus The fortuitous finding of hydrochloric acid in the aspirated cyst fluid offers an important preoperative diagnostic clue Another possible lead is the presence of other congenital anomalies of the skeleton or the intestinal tract (intestinal diverticula, enteric cysts in the mesentery) with a mediastinal enlargement In some instances actual peptic ulceration of the mucosa lining the cyst has taken place in turn perforating into a bronchus

Many of the conditions that produce enlargement of the mediastinum but which are not primary mediastinal tumors (Group B according to Nelson Shefts and Bowers) are discussed elsewhere In this regard the reader is referred to the discussions on aortic aneurysms (p 296) cardiac aneurysms and metastases (p 270) persistence of the left superior vena cava (p 301) pulmonary artery segment enlargement and aneurysms (p 280) a dilated azygos or hemiazygos vein [105 d] and buckling of the aortic

nodular goiter was mistaken for an aortic aneurysm or a malignancy, particularly when the I^{131} uptake was not clear cut [1054i] Practically all thoracic surgeons have found that it is only the rare substernal thyroid indeed which cannot be removed via the usual thyroidectomy approach

The cause of *mediastinal granuloma* remains an enigma in most instances Tubercle bacilli can be recovered from these lesions only rarely (None were found in 16 cases carefully studied by culture at the Mayo Clinic) It apparently results from the coalescence of a number of infected lymph nodes, which process in turn is followed by considerable cystic necrosis [1054f] This lesion is typically found as a smoothly oval or rounded, lobulated mass adjacent to the trachea and protruding into the right chest This position is indicative of the predilection for involvement of those nodes that are located in the area where the azygos vein joins the superior vena cava Many of these lesions also exhibit a central calcific stippled effect

With the use of the periodic acid Schiff stain, Gomori's methenamine-silver nitrate stain, and the combination of positive histoplasmin and negative tuberculin skin tests, it has been shown that histoplasmosis may be the cause of mediastinal granulomas much more frequently than was previously thought to be the case [1054j]

One should also bear in mind that subcarinal mediastinal granulomas can produce esophageal obstruction [1054h] In addition to such an obstructive esophagopathy and tracheobronchial obstruction, mediastinal fibrosis of granulomatous origin might occlude much of the venous return from both lungs, resulting in pulmonary hypertension and progressive ventricular failure [87a]

There is little doubt that "*tuberculomas*" can affect the hilar lymph nodes in the absence of any clinically recognizable pulmonary involvement [1054g] Thoracic surgeons and pathologists alike are becoming more aware of the fact that this diagnosis has been incorrectly made in a number of instances solely on the basis of finding a discrete lesion in the mediastinum containing *a sterile putty like material* Thymic cystadenomas are particularly prone to be so confused [1053d]

Benign and malignant *tumors of the thymus* and *thymic cysts* are causes for obscure mediastinal enlargement [1055a, b] Here again, sudden enlargement with symptoms may take place due to the occurrence of hemorrhage within the thymus In view of the location of the thymus just beneath the sternum rapid deceleration of the body might traumatize a pathologic thymus gland (carcinoma or cyst), with the subsequent occurrence of hemorrhage into this organ and severe precordial pain Breckler has reported upon two *such cases* [1064] *In fact the presence of extensive cystic formation* may render identification of thymic tissue within the tumor very difficult The relationship of thymic tumors to both obscure anemias (p 345) and to myasthenia gravis (p 371) is considered elsewhere The considerable reservation with which the diagnosis of an enlarged thymus should be made in young children on the basis of only one set of films is again stressed

Angiomas are rare causes for mediastinal tumors and are practically never diagnosed preoperatively They may take the form of a

When *metastases from malignancies of the abdominal organs* involve the para aortic lymph nodes, they often continue their extension through the diaphragm They can accordingly present as either a mediastinal or a (left) cervical lymphadenopathy

There is usually little difficulty in making the diagnosis of a *mediastinal abscess* when the history of instrumentation, trauma or ingestion of some corrosive substance is obtained, or when a foreign body is found in the esophagus Instances have occurred wherein an *empyema of the mediastinum* developed following a pneumonia but was not detected under the cover of antibiotic therapy These patients then presented themselves with a mediastinal mass sometime later Brief mention is made of the possibility of mediastinal involvement as a result of the extension of an osseous infection due to tuberculosis or syphilis

A *tumor of the bony thorax* usually a chondroma or a chondrosarcoma, can grow inwardly into the mediastinum with little or no discernible change in the rib detail shown by x ray [1053d] There need be no externally visible or palpable tumor or deformity The chondrosarcomas tend to be discrete, homogeneous masses, and most frequently make their appearance in the posterior position Extra abdominal desmoid tumors and keloid like tumors of the thoracic wall might be the result of either previous surgery upon or trauma to the chest wall [1058d]

Diaphragmatic herniae via either congenital or acquired defects of the various foramina have simulated mediastinal tumors on a number of occasions—at times much to the chagrin of the attending thoracic surgeon [1053d] Particular emphasis is placed upon the herniation of omental fat and other non gas-filled viscera through defects of the Morgagni type which are located anteriorly and parasternally (A laparotomy rather than a thoracotomy is usually the preferred surgical method in this disorder) There is a wide variety of potential herniated structures, as for example, the entrance of duodenal and jejunal diverticula into the posterior mediastinum

An *intrathoracic meningocele* may simulate various primary mediastinal tumors or cysts [1058e] The lateral chest film in these cases typically reveals erosion of the posterior margin of the vertebral body, along with a widening of the intervertebral foramen The clinician is reminded that these changes may also be noted in cases of neurogenic ' dumbbell tumors, wherein a portion of the tumor is intraspinal and the remainder is intra thoracic

The author has been impressed by the frequency with which *cardiospasm* (mega esophagus) can present radiographically as a mediastinal tumor The presence of a crescentic air meniscus at the superior aspect of an enlarged mediastinal shadow should immediately suggest the possibility of achalasia [1058]

CONSIDERATIONS IN THE DIAGNOSIS OF LIVER TUMORS

Somewhat similar considerations apply in the case of neoplasms involving other organs most notably the liver and kidneys The constantly developing insight into both the lobar and circulatory anatomy of the liver, along with the increasing feasibility of removing hepatic neoplasms

arch (p 300), the descending aorta (p 300), or the innominate artery (p 301) Attention is also directed to the following possibilities

Malformations of the manubrium sterni and other chest wall anomalies[1154]
A right-sided aortic arch[1057]
Esophageal diverticula
The dilated esophagus in cardiospasm[1058c]
Anomalous pulmonary venous drainage (*vide infra*)
Other venous aneurysms or varicosities of the mediastinum[1058a]
Lymph node hyperplasia[1056c]
A large dilated left auricle
Coarctation of the aorta with poststenotic dilatation
An atelectatic azygos lobe
Metastatic malignancy (*vide infra*)
Hydatid cyst of the mediastinum
Intrathoracic meningocele (*vide infra*)
Diaphragmatic hernia (*vide infra*)
Eventration of the diaphragm
Erythema nodosum[930, 982]
Mediastinal abscess (*vide infra*)
Chest wall tumors (*vide infra*)
Mediastinal collagenosis
Retropleural hematoma following sympathectomy[1279b]

Every clinician has been fooled by an *aneurysm* of some great mediastinal vessel which simulated either a mediastinal tumor or a lung tumor This can be appreciated more readily in light of the atelectasis and pulmonary infection that is prone to result from the pulmonary compression, the persistent and intense pain due to the erosion of bone, and the dysphagia resulting from pressure onto the esophagus As was indicated earlier, there may be such a dense laminated clot within the lumen of the aneurysmal vessel that considerable difficulty might be encountered in positively identifying the enlargement as being of a vascular nature, even with the use of fluoroscopy, angiography, and kymography

A *right sided aortic arch* is one of the most common anomalies of the great vessels and is usually asymptomatic It is most often discovered as a confusing mediastinal shadow on routine chest films [1057] This entity must not be confused with dextroposition of the aorta which represents a completely different anomaly

In addition to the fact that *congenital valvular pulmonic stenosis* is not at all rare in the third and fourth decades, it is also pointed out that the degree of poststenotic dilatation of the pulmonary artery in these patients may be so great as to suggest a left hilar mass [878a]

The diagnosis of *anomalous pulmonary venous drainage* may be suggested even prior to cardiac catheterization and angiocardiographic studies by the "figure of 8" configuration of the heart and mediastinum in the P-A projection, and the associated evidence of large anomalous draining veins from the right lower lobe crossing in front of the esophagus to the left side of the mediastinum [1058b]

While they are not in the strict sense mediastinal tumors, *bronchogenic carcinomas* actually constitute the most commonly encountered intrathoracic neoplasm [461] The oat cell type of tumor, in particular, tends to frequently invade the mediastinum

effects The *juvenile nasopharyngeal fibroma* may prove fatal because of its invasiveness while histologically having the appearance of an innocuous lesion

Thymomas have been associated with either refractory anemia or myasthenia gravis (pp 190 and 371)[1063] Of the six cases in one series in which the thymoma was surgically removed, the anemia was cured in two, relieved in two and unaffected in two[1063a]

Another benign non neoplasm that occasionally results in unusual manifestations by virtue of its unique growth, spread, and invasion is that of *endometriosis externa*[1065] Endometrial transplants from either the tubal spill or from rupture of the cysts can seed the pelvic peritoneum rectum, mesorectum ileum, sigmoid, cecum, appendix ureter, urinary bladder hernial sacs, and the skin, particularly in the region of the umbilicus and in old operative abdominal scars Consequently, bowel obstruction and bleeding urinary symptoms and bleeding, backache and other phenomena may occur, along with classical features of increasing dysmenorrhea in sterile women

Extensive rectal endometriosis has been observed in the absence of ovarian or general pelvic involvement it is suggested by the lack of mucosal or regional node involvement Endometrio is prior to the onset of the menstrual period may also mimic appendicitis Another example of the unusual syndromes this disease can produce is that of unilateral or bilateral lymphedema due to the occlusion of the iliac veins[1065c] Several instances of ureteral obstruction and eventual nonfunction of the kidney due to an intramural endometrial lesion which necessitated a nephro-ureterectomy, have been reported[1065d] There have been reports of recurring hemorrhages from the lungs the tracheobronchial tree and the nose (vicarious menstruation) due to extragenital endometriosis[1065e]

The clues to this diagnosis are, as always, the exacerbation of symptoms at menstruation and the finding of hard, fixed nodules in the pelvis The diagnostic accuracy of the examination is enhanced by a simultaneous rectal and vaginal examination just prior to the menstrual period

There are a number of true tumors that are locally invasive in spite of appearing benign histologically These include the chemodectomas[897] the mediastinal lymphangiomas and hemangiomas[1055c d] bronchial adenomas[1068 1069] and carcinoids of the small intestine[10 0 1073]

PSEUDOMYXOMA PERITONEI AND PERITONEAL MESOTHELIOMA

Another interesting but uncommon condition that might be mistaken for advanced abdominal carcinomatosis from either the bowel or ovary is *pseudomyxoma peritonei* This is actually an unpredictable complication occurring in the course of a variety of intra abdominal diseases among which are mucocele of the appendix omphalomesenteric cyst, and intestinal diverticulum[1067] Prolonged periods between the removal of an ovarian cyst and the appearance of this gelatinous exudate (which is partly free and partly encysted) are on record

The diagnosis may be suspected by the presence of a silent nonpainful and chronic swelling of the abdomen in the absence of cachexia and fol

(both primary and metastatic), has increased the clinician's awareness and responsibility in the diagnosis of certain benign and malignant tumors of the liver[1060]

A case in point concerns the occurrence of pedunculated masses (*hepatoadenomas*) arising from the liver These are usually the result of the reparative process taking place within areas of liver cell injury and destruction (usually postnecrotic cirrhosis or subacute hepatitis) In two separate reports (each consisting of four such cases) and from a review of a number of similar cases in the literature, it was found that the pre operative diagnoses of hepatoma, hamartoma, adenocarcinoma, and other neoplasms had been universally entertained[1061] Similarly, *cholangioade nomas* that originate from the bile ducts and usually appear as small sub-capsular collections of proliferating bile duct epithelium may closely sim ulate metastatic deposits until their true nature is ascertained histologically *by means of biopsy*[1061b]

As in the case of certain bronchogenic carcinomas, the appearance of *calcification within a liver mass* does not necessarily rule out malignancy The presence of a finely granular hepatic calcification has been a note-worthy feature of certain metastasizing carcinomas originating in the rec tum or the sigmoid[106] A number of clues to the early diagnosis of an obscure intrahepatic malignancy appear in Group III, of which the finding of a *partial biliary tract obstruction* (elevated serum alkaline phosphatase and marked BSP retention) in the presence of both a normal serum bili rubin level and normal parenchymal function studies is noteworthy (p 87)[324]

As previously indicated, in patients with either cirrhosis of the liver or hemochromatosis, the presence of a palpable mass, upper abdominal pain, a high right diaphragm and a rapid downhill course should suggest a complicating carcinoma (p 96) Hypoglycemia, hyperthrombocyte-mia a venous hum or murmur over the liver, and early jaundice due to a bile duct carcinoma developing at the hilum of the liver may be additional manifestations[1015] Inasmuch as surgical removal of certain liver carci nomas has occasionally been successfully performed, this diagnosis is no longer solely an academic matter

BENIGN TUMORS INDUCING SYSTEMIC EFFECTS

Several examples of the systemic effects of benign tumors include *the Meigs Cass syndrome* due to an ovarian fibroma (p 35), *myxoma of the heart* in the mitral valve area (p 256), benign central nervous system *tumors in the region of the third ventricle and pituitary gland* (p 373), and *the endocrine gland adenomata* (p 18–30) The significance of *pancreatic tumors* in relationship to the production of *hyperinsulinism* was elaborated upon under Group I (p 19) Other pancreatic tumors, possibly composed of alpha gamma or delta cells result in *the Zollinger Ellison syndrome* This disorder is characterized by the occurrence of bizarre multiple peptic ulcer ations that prove refractory to medical and surgical treatment (p 20)[63]

The metastasis of *echinococcal daughter cysts* was previously cited (p 174) A benign tumor that is strategically located, as *at the ampulla of Vater* or *in the region of the cervical spinal cord*, can also produce profound

large quantities of serotonin metabolites, the primary tumor originated in the lung as a bronchial adenoma of the "carcinoid type"[1069b]

Brief mention is also made of the widespread *papillomatosis of the segmental bronchi* that can follow the long standing presence of laryngeal papillomas (Papilloma of the larynx represents the commonest cause of prolonged hoarseness in children) While many of these tumors probably arise *in situ*, there may be some element of seeding due to previous laryngeal surgery Extensive bronchial papillomatosis is often complicated by severe recurrent pneumonitis massive hemoptysis (with an associated fibrinolysis described in one instance) and possibly the development of a papillary squamous-cell carcinoma[453] Falsely positive results of cytologic studies of the bronchial secretions have been reported (that is, without any malignant change at autopsy)

CARCINOID TUMORS OF THE SMALL BOWEL

Another case in point is that of carcinoid tumors of the small bowel These lesions have mimicked hepatic disease pancreatic dysfunction and primary cardiac disorders in part due to the prolonged survival of these patients even when extensive metastases are present[1070 1073] The behavior of ileal carcinoid tumors differs from that of appendiceal carcinoids, which are usually found in younger patients simulating appendicitis While appendiceal carcinoids possess an unusually low grade of invasiveness, all extra appendiceal carcinoids should be considered malignant and reported in terms of invasiveness In contrast to other intestinal neoplasms carcinoid tumors rarely ulcerate

Thorson and his colleagues have reported on the syndrome of valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects) edema, ascites diarrhea peripheral vasomotor symptoms and bronchoconstriction resulting from this tumor and its visceral metastases[1071] Excluding rheumatic valvular lesions, definite isolated lesions of either the pulmonic or the tricuspid valve, or both were encountered in 31 of 53 cases in one review[1072b]

The earliest manifestations may be apparent as a transient and changing flushing of the skin—possibly associated with hypotension—and later mingling with patches of cyanosis and white blotches In fact it has been difficult to distinguish these vasomotor phenomena from symptomatic ovarian insufficiency in some patients, a problem further complicated by the occasional striking psychiatric manifestations of this tumor The intestinal hypermotility can simulate sprue dysentery, and functional gastrointestinal disorders An increased incidence of gastric and duodenal ulcers has also been observed in association with metastatic carcinoid[107]

The cutaneous vasomotor manifestations of metastatic carcinoid tumor of the small bowel are depicted in Figure 7 (Atlas page 6)

Both the production of serotonin by the tumor and the previous partial resection of the bowel that many of these patients have had account in large measure for the diarrhea This substance is not only highly vasoactive, but it is also a potent stimulant of the smooth muscle in the gastrointestinal tract and bronchi It is hoped that the markedly elevated

lowing a history of repeated attacks of abdominal pain (presumably due to recurrent appendicitis) Not only is this entity rarely considered before surgery, but the diagnosis is also infrequently correctly made either by the surgeon at laparotomy or by the pathologist Even in a female patient with an ovarian cyst, the appendiceal tumor must be sought out since faulty intestinal absorption, debility, hypoglycemia, pressure phenomena, and death will otherwise ensue

Clinicians who are confronted with a vague symptom complex of varying duration which is culminated by the onset of a progressive ascites should consider the possibility of a *peritoneal mesothelioma* In 11 well documented cases that were reviewed by Pendergrass and Edeiken, other abdominal manifestations (pain, nausea, vomiting, and a change in bowel habit), weight loss, and tender nodules were also encountered[1066a] The lesions are most numerous on the mesentery, and tend to spread by direct extension to the thorax and the viscera

The value of a careful cytologic examination of the cell fluid is at once apparent in establishing this diagnosis (p 788) There may be some confusion encountered by the pathologist, due to the variable expressiveness of the multipotential malignant mesothelial cell (i e, it can assume either an epithelial or fibroblastic appearance with the formation of collagen or reticulin fibers)[1066b] In spite of the presumed radioresistance of this malignancy, there have been several gratifying remissions induced both by x-ray therapy and following the intraperitoneal introduction of a number of radioisotopes

BRONCHIAL ADENOMAS AND BRONCHIAL PAPILLOMATOSIS

As was noted above, a tumor that is histologically "benign" can occasionally produce unusual syndromes This may result from either the presence of metastases or the release of physiologically active substances One striking example of this phenomenon relates to *bronchial adenomas*

Although these slowly growing tumors were generally regarded as benign for many years it now appears more accurate to view them as low grade malignant tumors In one composite group of 86 patients, Moersch and Harrington found evidence of metastases locally, to the mediastinal nodes, or widespread throughout the body in approximately 10 per cent[1068a] In another series of 60 patients with bronchial adenoma who were subjected to resection by Overholt and his colleagues, the malignant potential was evidenced by lymph node and distant metastases in 15 per cent of the cases[1068b] Fortunately there is a very high cure rate in patients with bronchial adenoma with little correlation between resectability or curability and the duration of symptoms

The high incidence of delayed hepatic metastases (which at times do not become manifest until many years after an apparently curative pneumonectomy) bears emphasis While the cylindroid form of bronchial adenoma is supposedly more invasive and more apt to give rise to metastases, it should be stressed that the carcinoid form has not infrequently behaved in a similar fashion[1069a] In 3 of 20 patients with carcinoid who excreted

GROUP XII

Disorders of the Nervous System

THE FUNCTIONAL DISORDERS

General considerations—clues from observation and the psychiatric interview

The Hyperventilation Syndrome

Conversion Reactions

The Depressions

Schizophrenia

CONSIDERATIONS RELATING TO THE IMPORTANCE OF THE CONCEPT OF DISEASES OF ADAPTATION IN OBSCURE ILLNESS

ORGANIC ILLNESS SIMULATING FUNCTIONAL DISEASE

THE MUNCHAUSEN SYNDROME

EPISODIC DISORDERS OF THE CENTRAL NERVOUS SYSTEM

Multiple Sclerosis

Small Strokes

Meniere's Disease

Migraine

Epilepsy

The Narcoleptic Syndrome

The Thalamic Syndrome

CEREBRAL INFARCTION AND CEREBROVASCULAR INSUFFICIENCY

CONVULSIONS

Withdrawal Seizures

Convulsions in Later Life

BRAIN TUMORS

OTHER DISORDERS RESULTING IN INCREASED INTRACRANIAL PRESSURE OR SIMULATING BRAIN TUMORS

Pseudotumor Cerebri

Emphysematous Encephalopathy

"Hydrocephalic Crises

Subacute and Chronic Subdural Hematoma

Cysticercosis Cerebri

urinary levels of the serotonin metabolite, 5 hydroxyindoleacetic acid, will continue to materialize as a relatively simple and specific test for metastatic argentaffinoma (p 702)[1073] This determination has already proved its unique reliability over liver biopsy In fact, specimens of liver tissue were initially diagnosed as "hepatoma" in several of these patients

The results of metabolic tracer studies dealing with the precursor relationship of dietary tryptophane to 5 hydroxyindoles in man are of interest in explaining this biochemical observation As much as 60 per cent of dietary tryptophane is converted to urinary 5 hydroxyindoles in this disorder, in contrast to only the 1 per cent so metabolized normally If adequate niacin cannot be elaborated from tryptophane in the metastasizing carcinoid syndrome (as a result of the great diversion of this amino acid into the production of 5-hydroxy-tryptamine), pellagra might ensue with the characteristic dermatitis, diarrhea, and dementia[1072c] As in the case of a patient with pheochromocytoma who has paroxysmal attacks, the injection of histamine intravenously into patients with malignant carcinoid may reproduce both the clinical syndrome and the hyperserotonemia (p 829)[1073c]

Many presenting complaints which might suggest organic disease are due to *the hyperventilation syndrome, conversion reactions depressions,* and *"ambulatory" schizophrenia*[1074, 1075] These disorders commonly occur in medical practice and can very readily mislead the unwary physician particularly when superimposed upon coexisting diseases For example, patients with mild spontaneous hypoglycemia or postural hypotension are more prone to experience the complete clinical pattern of their 'weak spells after hyperventilation Such experiences are encountered daily in a consultation practice particularly by those interested in the so-called psychosomatic diseases They serve to once again emphasize the potential error of psychiatric diagnosis by exclusion since one is not dealing with either/or situations This entire issue becomes a greater problem in direct proportion to the degree of specialization no matter what the field

Because of the quantitative magnitude of the problem posed by *manic depressive disease,* the inexactness in making the diagnosis, and the extraordinary frequency with which this condition is missed, clinicians should bear it in mind at all times when confronted with vague, long standing symptom complexes In actual practice one encounters the textbook picture of manic excitement alternating with retarded depression much less frequently than the more subtle manifestations of this disease such as insomnia with early morning waking Williams has correctly pointed out that many instances of depression tend to present themselves as anxiety states characterized by tension, weakness dizziness, and evidences of autonomic imbalance[1075d] The physician would do well to appreciate the prolonged periods over which the grief and sorrow of a 'bereavement reaction' may persist in some individuals however before committing the patient to a definitive diagnosis of a pathologic depression

A recent comprehensive study tends to refute the clinical impression that the multiplicity of medical symptoms related to the head, the cardiovascular system the gastrointestinal system the genitourinary system and the neuromuscular system is any greater in this disease than their frequency and distribution among a "control group of medically sick patients[1075e] Nevertheless the universal incidence of serious psychological and mood disturbances which manic depressive patients experience—particularly poor concentration irritability and abnormal mood—contrasts with the infrequency of these phenomena in other patients These individuals tend to be compulsive and to consume alcohol for its therapeutic effect on their mental state

The difficulty that occasionally arises in deciding whether a patient is truly a *compensated paranoid* or an *early schizophrenic* and whether certain hallucinations are organic or primarily psychotic may be considerable This is particularly apt to be the case when the patient appears to possess some insight into his condition Sometimes it is necessary to observe the patient for years in order to definitely differentiate these conditions from mixed anxiety, hypochondriacal and compulsive states[1075d] The physician should avoid the assumption that emotionally disturbed patients can readily perceive certain obvious cause and effect relationships in the genesis of their neurotic personalities

With experience, the clinician becomes aware of a number of *clues*

CENTRAL NERVOUS SYSTEM MANIFESTATIONS OF SYSTEMIC DISEASE
"Acute Brain Purpura"

MYASTHENIA GRAVIS

AMYOTROPHIC LATERAL SCLEROSIS

SYNDROMES DUE TO INVOLVEMENT OF THE HYPOTHALAMUS AND THIRD VENTRICLE

POTENTIALLY TREATABLE SPINAL CORD DISORDERS
Combined System Disease
Syphilis
The Metabolic and Infectious Polyneuropathies
Herniated Intervertebral Disc
Traumatic Lesions
Spinal Cord Tumors
Myeloma
Radiation Myelitis
Staphylococcal Spinal Epidural Sepsis
Dissecting Aortic Aneurysm
Complications of Spinal Anesthesia
Spinal Cord Extradural Hematoma
Decompression Sickness
Extramedullary Hematopoiesis

THE POLYNEUROPATHIES—DIFFERENTIAL DIAGNOSIS

DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM
"Primary Autonomic Insufficiency"
Dysautonomia

TUMORS OF THE VAGUS NERVE

THE NEURODERMATOSES
Neurofibromatosis (von Recklinghausen's Disease)
The von Hippel Lindau Disease
The Sturge Weber Syndrome
Tuberous Sclerosis

CONSIDERATIONS IN THE DIAGNOSIS OF "FUNCTIONAL" AND ORGANIC ILLNESS

"Functional" psychiatric disorders of the central nervous system should be kept in mind when one is confronted with obscure chronic symptoms, especially if changes in the personality have occurred, however slight An indication of the enormity of this problem is evidenced by a recent review of 1000 unselected diagnostic problem cases which were referred to one consultation service A primary or significant secondary diagnosis of a psychiatric disorder was made in 81 4 per cent[1076] Moreover, psychiatric consultation was usually requested only when no overt organic factors were found

apparent somatic delusions (as "ants crawling in and out of my skull') warrants further energetic diagnostic studies of the central nervous system

6 The physician must not be completely influenced by his own emotional prejudices that stem from a knowledge of the patient's past history[1077b] This point bears repeated emphasis in the case of chronic alcoholics or where compensation has been an issue These two groups of patients, in particular have often been deprived of otherwise indicated diagnostic efforts and specific therapies because of such bias

THE CONCEPT OF DISEASES OF ADAPTATION

Many thoughtful clinicians are deeply impressed with the scientific basis offered by Selye and others as a logical foundation for explanation at least in part, of the many so-called "diseases of adaptation in which no one specific biochemical or infectious cause has been (or may ever be) found As mentioned under the collagen diseases it is admitted by all that a similarity of histopathology does not necessarily imply identity of pathogenesis Nevertheless one cannot remain uninfluenced by the fact that emotional stress—particularly long standing frustration and fear—as well as physical and other types of stress can predictably induce or condition polyarteritis nephro clerosis, nephrosis hypertension apoplexy and gas trointestinal ulcers in experimental animals These effects apparently occur through common hormonal pathways which result in the aptly designated stages of resistance and exhaustion ' The validity of this concept has been demonstrated further by the production of similar lesions by the naturally occurring hormones particularly the mineralocorticoids (includ ing aldosterone)

On the other hand the necessity for a careful and skeptical evaluation of emotional stresses as significant determinants of ' resistance in a variety of disorders has been independently pointed out by several observers[1078] They emphasize the great incidence of "stress in control population groups, and the wide variations of general susceptibility to illness exhibited by certain individuals in any particular group Furthermore one must not make the error of regarding all forms of stress as pathologic since stress (both physical and mental) is obviously essential for the proper condition ing of the body s homeostatic and adaptative mechanisms

The appropriateness of including this concept in a treatise on practical diagnostics—and more so within the discussion of central nervous system disorders—may be properly questioned It is the author s contention that much diagnostic and therapeutic reward is to be reaped in understanding difficult case material by grasping this lead, by attempting to define these "nonspecific ' manifestations of emotional stress and by relating them to the concept of the general adaptation syndrome' in light of the longitudinal past history the family history and the situational or ideological background of the patient To cite but one such provocative example is the demonstration by several authors of the profound basic relationship that was observed between psychological upheaval and scleroderma in several individuals studied[966] It has been aptly stated that "both the telescope

that suggest the probability of a significant neurosis during the initial interview with a new patient. These include the long lists of complaints that have been written down, the continual wearing of dark glasses, the volunteering of the history by a patient's wife before he can speak, and certain features that become apparent during the examination. Only the following few of the latter will be recounted here—marked objections to being examined or undressed, the complaint of considerable pain during the taking of the blood pressure, excessive blushing and sweating, a labile blood pressure, the persistence of a rapid pulse with frequent premature beats, nail biting, shaving of the body hair in men, women with either elaborately pencilled and plucked eyebrows, or black hair that is bleached to flashy shades of platinum or blond, numerous abdominal incisions ("railroad tracks"), persistent belching, overactivity of the gag reflex, and frequent tics or twitches of the eyelids.[1074b]

To the clinician engaged in the practice of "comprehensive medicine" and to the consultant—as well as to the psychiatrist—*the critical unbiased psychiatric interview* can cast much doubt on a previous diagnosis of neurosis or psychosis. When an organic condition exists and is adequately treated—as in the case of myxedema—the persistence of psychotic symptoms in the absence of a convincing background for emotional illness should necessitate further diagnostic study. In a brief but very appropriate discussion of the "Psychiatric Interview as [a] Tool of Medical Diagnosis," Faucett has made the following pertinent observations which bear repetition and elaboration.[1077]

1. The emotional impact of a previous (and correct) diagnosis of multiple sclerosis or some other form of organic brain disease may terrify certain patients into experiencing additional bizarre psychiatric symptoms.

2. The prominence of what superficially appears to be motivation for secondary gain may be the basis of an erroneous referring psychiatric diagnosis. One such classical instance is that of a wife developing spells of coma prior to her husband's anticipated fishing trips. It developed that she actually had an insulinoma and that on each of these occasions, she did not eat breakfast. Secondary gain commonly makes its appearance *only* after the primary psychiatric or organic illness is already well established.

3. Neurotic illness usually does not develop solely because of minor situational difficulties. Rather, it is the aftermath of an attempt by the patient to achieve some measure of adaptation in the face of intolerable, unconscious emotional conflicts. The latter can often be clearly identified.

4. When the patient with an apparent depression does not exhibit certain important and characteristic features of this disorder, such as an endogenous loss of self esteem and the presence of self depreciation, the physician should be on his diagnostic guard. The same consideration applies when there appears to be no history of early emotional deprivation or previous episodes of depression.

5. The clinician and psychiatrist alike should constantly appreciate the fact that verbal behavior and descriptions couched in bizarre language are at times both inadequate and misleading evidences of the patient's basic problem. For example, the absence of paranoid ideation and other psychotic elements in the behavior of an individual who is experiencing

such scientifically meaningless terms as "degenerative," "sclerosis" "epilepsy," "schizophrenia" "psychosomatic," and "dystrophy will ultimately be found This has already been partially achieved in the case of selective brain injury stemming from the effects of manganese, carbon monoxide, copper, and other noxious agents

The *value of careful psychometric testing* deserves occasional re-emphasis when it is difficult to evaluate or to separate the neurotic and organic components of a given symptom complex[108, 1083] The Rorschach test in combination with the other psychometric procedures listed in Part II (p 773) is all too often neglected or minimized even by psychiatrists and neurologists These techniques may offer fairly conclusive and objective information about the degree of neuroticism or the degree of organicity in a particular case This is obviously of unique value when the entire future of a bread winner rests upon a correct diagnosis of cerebral atrophy, post-traumatic syndrome, or other forms of organic "chronic brain syndrome"

A listing and analysis of the studies which have been helpful in evaluating pathologic conditions of the central nervous system is presented in Section VIII of Part II

THE MUNCHAUSEN SYNDROME

There are certain types of patients whose personality structure is such that the unwary physician—especially house officers in large municipal hospitals—will have considerable difficulty in fathoming the nature of their presenting disorders These situations evolve either for want of a complete history as a result of distortion or concealment, or because of a habitual falsification of the history and clinical picture (the Munchausen syndrome) In the first category are included the malingerers and drug addicts who may variously present with factitious fever (p 104) exogenous hyperinsulinism (p 20) septic pulmonary embolism (p 129) and a right sided endocarditis (p 117)

Extreme instances of the pathologic falsifier of illness who is a perennial migrating problem patient and who subjects himself to repeated hospital admissions and abdominal operations are infrequent[369b] Nevertheless, diagnosticians should be aware of the many facets with which less striking forms of such psychopathic paranoid behavior can present The following five ramifications of the so-called Munchausen's syndrome (named after the extravagant and fascinating tales of adventure and travel erroneously attributed to the raconteur Baron Munchausen) deserve mention at this point (1) the abdominal type—characterized by the patient undergoing repeated laparotomies and then often signing out before wound healing is established (2) the bleeding type—characterized by the patient dramatically presenting himself at emergency floors with spectacular but spurious hemoptysis epistaxis hematuria or gastrointestinal hemorrhage, (3) the neurologic type—characterized by bizarre (but at times quite convincing) epileptiform episodes anesthesias, fainting spells, and even apparent meningeal irritation (4) the cutaneous type—characterized by the patient provoking various lesions (even an exfoliative dermatitis) by the use of chemicals or other agents, and (5) the anginoid type—as has been simulated by habitual diaphragmatic flutter[86 a] These individuals charac

and the retrospectoscope are at times more rewarding than the microscope."

ORGANIC ILLNESS SIMULATING FUNCTIONAL DISEASE

The reverse situation to functional disease simulating organic illness also applies, namely serious illness presenting as a psychoneurosis.[1079] This is a fact to which most gastroenterologists who treat "psychophysiologic gastrointestinal reactions" can readily attest. The frequent association of gastrointestinal ulcers and other disorders with various neurologic diseases (*vascular accidents, tumor, trauma, infection*) has been repeatedly affirmed.[1080] It is the rare physician, indeed, who has not been misled by the neurotic patient with unrecognized organic disease whose last frequent "cries of wolf" went unheeded.

There is a wide spectrum of profound psychiatric aberrations that may result from *malnutrition* in the elderly patient, ranging from slight moodiness, confusion, and depression to the extremes of dementia and psychoses.[1300] One must accordingly be sure that the patient has received the benefit of a proper diet and vitamins before placing the defeatist label of "hardening of the arteries" or "senility" on these individuals. The clinician is once again reminded of the cerebral manifestations of *pellagra*, since paranoid behavior with mania or delusions of parasitosis have been observed to respond promptly to antipellagrous therapy (p. 43).[140] Either severe mental changes or a frank psychosis may be the presenting manifestations of *sprue*, another profound nutritional disorder which often remains undiagnosed for prolonged periods (p. 46).[153d]

The central nervous symptoms and manifestations of *hypoglycemia* are so varied and profound (loss of consciousness, confusional states, temper outbursts, extreme depression, motor or sensory loss in limbs, stupor, amnesia, clonic convulsions, tremors, negativism) that such misdiagnoses as idiopathic epilepsy, acute alcoholism, brain tumor, hysteria, psychosis, and anxiety neurosis are commonplace.[51b] *Bizarre behavior in the morning, in particular, should lead one to search for a pancreatic adenoma* (p. 19).

Addison's disease (p. 13), *parathyrotoxicosis* (p. 23), *hypothyroidism* (p. 16), *Sheehan's syndrome* (p. 32), *polycythemia vera* (p. 188), *cerebral metastases* (p. 363), *carcinoma of the pancreas* (p. 329), *aortic stenosis* (p. 258), *brucellosis* (p. 156), *tropical anhidrotic asthenia* (p. 528), and *porphyria* (p. 61) are several other diseases that have already been mentioned as occasionally simulating severe neurotic or psychotic illness. Many cases of apparent schizophrenia and other psychoses have been subsequently found to be due to *bromide intoxication* (p. 64).[229] Atypical psychiatric manifestations accompanying intellectual impairment, tremor, rigidity, and other pseudobulbar signs in a young patient merit careful search for the Kayser-Fleischer rings of *hepatolenticular degeneration* (Wilson's disease).[1081]

This formidable (but obviously incomplete) list of disorders that can produce striking psychiatric manifestations also serves to point out the many unknown realms in both neurology and psychiatry. Here again, one must be cognizant of the limitations of terminology. It is not at all unlikely that a factual basis for many diseases which are at present categorized by

1 The diagnosis of multiple sclerosis is not ruled out when some presumptive manifestation has once asserted itself merely because no further episodes take place for several years

2 The absence of well defined remissions and exacerbations does not rule out this disorder

3 The presence of a normal spinal fluid (including the colloidal gold curve) is compatible with this diagnosis

4 The occurrence of pain and level signs are not inconsistent with multiple sclerosis, but require further active investigation

5 The diagnosis should be made with reluctance when the initial features have their onset below the age of fifteen or after the age of fifty five

6 An individual within the twenty to forty four year old age group who experiences an attack of retrobulbar neuritis has a 40 to 50 per cent chance of developing multiple sclerosis within ten or fifteen years [1083e]

7 A relatively "specific' clinical feature (but which is encountered only in 10 per cent of cases of multiple sclerosis) is sheathing of the retinal veins in the midperiphery of the retina Neither the other vessels nor the retina itself are involved Rucker could establish no relation between this sign and the clinical form of the disease [1083f]

8 One must always be concerned about the diagnosis of a cord tumor or an arachnoiditis rather than lateral sclerosis or 'latent' multiple sclerosis when spasticity of the lower limbs is encountered in the absence of diplopia visual disturbances or bladder and sensory phenomena [1083g] In view of the ability of certain treatable high spinal cord lesions and brain stem lesions to mimic multiple sclerosis so closely, the author does not share the misgivings concerning the purported hazards of lumbar puncture myelography, and pneumoencephalography in attempting to rule out these disorders

9 The significance of an attempted differentiation between multiple sclerosis and an acute idiopathic diffuse demyelinating and necrotizing opticoencephalomyelopathy rests in the very poor prognosis associated with the latter process [1083h]

10 The precipitation of symptoms by emotional tension fatigue, and pregnancy could prove to be misleading in favor of a functional diagnosis

Meniere's Disease

One should be aware of the many pitfalls that might attend the casual diagnosis of 'Meniere's disease" For example it is possible for the vertigo to be present without either deafness or tinnitus or for the last two symptoms to precede the first vertiginous crisis [1085e] Furthermore inner ear vertigo must be differentiated from vertiginous epilepsy brain tumors, thrombosis of the internal auditory artery other cerebrovascular accidents, postural hypotension the carotid sinus syndrome pulmonary emphysema hypothyroidism and multiple sclerosis—in addition to disorders of the external ear, the middle ear and the eustachian tubes It is pointed out that the vertigo associated with brain tumors is usually continuous rather than intermittent and is not attended by deafness (except in the case of cerebellopontine angle tumors)

teristically become increasingly uncooperative and dissatisfied after a short stay in the hospital, and then (after considerable financial loss to the institution) solve the staff's problem by signing out

EPISODIC DISORDERS OF THE CENTRAL NERVOUS SYSTEM

The various episodic disorders of the central nervous system which undergo cycles of exacerbation and remission—with or without demonstrable organic or electrophysiologic disease—frequently perplex and elude the clinician *Multiple sclerosis*,[1033] *"small strokes,"*[1034] *atypical epilepsy*[1035a] *Meniere's disease*[1035b, c] and *migraine*[1035d] are all "great mimics in their own right With experience and observation, one develops considerable respect for the cardiovascular, abdominal, arthritic, autonomic and other manifold symptoms of each one of these aforementioned disorders The various considerations that should attend a diagnosis of postural hypotension are considered elsewhere (p 288)

Multiple Sclerosis

Every experienced clinician can probably recall a number of instances wherein he made an erroneous mental or non neurologic diagnosis in a patient who subsequently proved to have multiple sclerosis Such errors are not unexpected with this fairly common disorder (there being over 250 000 cases of the disease in the United States) since (1) the attacks are characteristically repetitive not only in space but also in time and (2) the diagnosis can *never* be made with certainty on the basis of a single isolated nerve dysfunction until there is definite evidence of several discrete lesions The mode of onset can be extraordinarily variable because of the disseminated nature of the discontinuous plaques throughout the central nervous system The crux of the diagnosis rests more in the word 'multiple than in the term sclerosis

With reference to the relative frequency of initial symptoms, ocular disturbances are encountered in 40 per cent, motor or sensory disturbances in the limbs in 30 per cent and derangements of equilibrium, speech bladder or psyche in 3 to 7 per cent[1033b] There may be only one minor symptom of such a transient nature at the onset of the illness however, that the physician may consider it to be purely a local phenomenon Such manifestations include blurring in one eye slight paresis or paresthesias of a single extremity or clumsiness of one hand Other presenting features include vertigo, tinnitus, emotional changes retrobulbar neuritis, dysfunction of the urinary bladder or rectal sphincters autonomic derangements, intense lethargy (due to a hypothalamic lesion) facial pain (due to a lesion in the descending trigeminal tract of the hind brain)—in addition to the classic evidences of spinocerebellar and corticobulbar pyramidal tract involvement Papilledema facial palsies headache, aphasia, hemianopsia, and convulsions are infrequent and unusual manifestations, but have been observed[1033c, d] Only the very advanced case will demonstrate the Charcot triad (scanning speech, nystagmus intention tremors)

Experience has also verified the accuracy of the following reservations concerning the diagnosis of multiple sclerosis[1033b, e]

ticular group of narcoleptics that the diagnosis may be very difficult to establish In the majority of cases, the narcolepsy begins in the second or third decade and precedes the cataplexy, at times by many years

Several of the possible diagnostic pitfalls merit brief attention When the patient characterizes his episodes of sleep as "attacks' or "blackouts,' they may be casually assumed to represent seizures or syncopal attacks The differentiation rests in large measure on the fact that these episodes are not paroxysmal and the patient can be readily aroused Similarly, the observation that the patient nods his head while drowsing can be misconstrued as a petit mal or akinetic seizure These individuals *rarely* have hypothyroidism but the complaint of chronic fatigue has misled unwary clinicians on many occasions in this direction Similarly, the physician should attempt to obtain a careful history in order to avoid stigmatizing the patient who complains of such fatigue with a diagnosis of psychoneurosis The associated visual or auditory hallucinations are often very vivid but may be present for years without any evidence of significant psychiatric disease developing Finally, with reference to the entity of sleep paralysis a number of these individuals have at one time or another been diagnosed as having myasthenia gravis or familial periodic paralysis when the physician was preoccupied with this isolated manifestation

Thalamic Syndrome

While the clinical picture of a mild thalamic syndrome is usually vague it may be well to deliberate upon this diagnosis when confronted with various obscure pains, numbness or hyperesthesia in elderly patients particularly if these manifestations are predominantly unilateral In addition to the sharp contralateral delimitation of severe spontaneous pain of the central type due to a lesion in the thalamus or its cortical connections there are frequently diminished cutaneous sensitivity disturbed deep sensibility and vasomotor trophic disturbances Hemiparesis may be either transient or permanent While the thalamic syndrome is usually due to local thrombotic phenomena it has also been described in association with cerebral embolism [1036b]

CEREBRAL INFARCTION AND CEREBROVASCULAR INSUFFICIENCY

The emphasis upon attention to episodic disorders of the nervous system is also distinctly wise in the case of both *cerebral vascular thromboses* and *nonthrombotic infarctions* affecting the 'silent' areas of the brain It is recalled that in over 60 per cent of the cerebral infarctions studied at postmortem examination no intra arterial thrombus can be demonstrated [1037] (On the other hand certain eminent neuropathologists believe that a vascular occlusion is almost always demonstrable by careful dissection and histologic study)

When confronted with a perplexing and chronic constellation of symptoms in patients past fifty, one should diligently attempt to uncover any associated subtle mental and personality changes of small strokes, as well as the more acute neurologic crises Among the e may be cited memory

On the whole, little fundamental insight is usually achieved by attempting to attribute greater significance to "subjective vertigo" (i e, wherein the awareness of the sham movement is referred internally), in contradistinction to "objective vertigo" While the terms of vertigo and dizziness are often used interchangeably, it is important to be sure that the patient is not experiencing "giddiness" or "light-headedness"*

Migraine Equivalents

From an extensive experience with the problem, both at the Lahey Clinic and subsequently in his private consultation practice, the author continues to be impressed with the numerous ramifications of "migraine equivalents" Many of these individuals have had every conceivable caption placed on their symptom complex by ophthalmologists, neurologists, neurosurgeons, gastroenterologists, and other physicians—particularly when headaches were not the prime feature of the disorder (as is often the case in postmenopausal women) The clinician who bears this diagnosis in mind when confronted with such a situation will have his astuteness rewarded by the profound gratitude of these highly gifted individuals who no longer must fear the possibility of harboring a brain tumor, a stroke, or some other dreaded lesion

Epilepsy

Many psychiatrists have encountered instances of behavioral and psychiatric disturbances or mental deficiency that ultimately proved to be due to "subclinical" epileptic seizures This correlation is most notably significant in the case of temporal lobe epilepsy When the sensory area and adjacent regions of the parietal lobe are injured, the patient may experience a host of localized sensory phenomena in the corresponding body part of the opposite side A number of manifestations due to "visceral epilepsy," including paroxysmal abdominal pain, may give little inkling of their intracranial origin for prolonged periods[1085a d e]

Narcoleptic Syndrome

Clinicians should also harbor considerable respect for the narcoleptic syndrome by virtue of the following (1) the diagnosis rests primarily upon a careful history, (2) it is a significant cause of obscure "fatigue" and "tiredness", (3) therapy is usually highly effective, (4) it is by no means an uncommon condition, and (5) the patient is constantly in danger from accidents if left untreated[1086a] Well over 300 cases of this disorder were diagnosed at the Mayo Clinic in a six year period The narcoleptic tetrad consists of narcolepsy, cataplexy, sleep paralysis, and hypnagogic hallucinations It is encountered in its complete form, however, in only one out of ten individuals with the disease

There is almost always some sustained drowsiness, even though a large number of these patients who fight a constant battle against sleepiness during the day will deny episodes of actual sleep It is in this par

*See reference 385 of Part II

The diagnosis of a *carotid artery occlusion* can on occasion be made without angiography by the inability to palpate the internal carotid pulse in the posterolateral pharynx or by the precipitation of unconsciousness when the opposite carotid artery is temporarily occluded[1091] It is quite likely that the cases of hemiplegia following carotid sinus manipulation which have been reported had previously had advanced carotid artery insufficiency The combination of a homolateral blindness and a contralateral hemiplegia should suggest an extracranial occlusion of the internal carotid artery with involvement of the ophthalmic artery[109] Mention was made of the thoracic outlet syndrome (p 222) as being contributory to pathologic conditions of the carotid vessels Determination of the retinal artery pressure by use of the Baillart ophthalmodynamometer (which is applied to the lateral surface of the sclera) may be of great value in the diagnosis of internal carotid artery occlusion (p 809)[109*b]

Reference was made earlier to the close clinical (and probably etiologic) relationship between carotid artery thrombosis and the so-called pulseless disease In the latter instance there is an occlusion of several of the main arterial trunks from the aortic arch (p 301)[9]

When a normotensive adult *under the age of forty years* experiences an *acute spontaneous cerebrovascular accident* it is the clinician s obvious responsibility to seek out an underlying systemic etiology Nevertheless the fact remains that premature arteriosclerotic vascular changes constitute the most common pathogenetic factor in this situation (as is the case in coronary occlusion affecting the young) Even so many physicians are reluctant to accept such an explanation for focal cerebral signs in their younger patients Thromboses of the internal or common carotid arteries in particular are apt to be frequently overlooked under these circumstances[1093]

In two series of 13 and 18 young patients in whom cerebral accidents had occurred and in whom hemorrhage, hypertension neoplasm and vascular anomalies were fairly well ruled out, the following causes were uncovered or considered[1094]

1 Diffuse arteritis and the collagen disorders—disseminated lupus erythematosus, polyarteritis scleroderma migratory polyphlebitis, Buerger s disease

2 Hematologic disorders—the purpuras hemophilia, fibrinogenopenia hypoprothrombinemia sickle cell disease, polycythemia vera thrombotic thrombocytopenic purpura

3 Infectious or postinfectious cerebral vascular accidents—pertussis measles influenza pneumonia typhus infectious mononucleosis malaria

4 Cerebral embolism—endocarditis rheumatic heart disease, myocardial infarction fat embolism

5 Intracranial venous thrombosis—postpartum and postoperative states following head trauma

6 Meningovascular neurosyphilis

7 Miscellaneous—carbon monoxide poisoning ergotism

Cerebral infarction and permanent brain damage have also resulted from the prolonged vasospasm occurring during severe migraine seizures[1095]

changes, a general "slowing up," carelessness, the fear of being alone, a loss of old interests vague discomforts in the chest or abdomen, burning of the tongue sleep disturbances, hypnagogic confusion, periodic breathing, a bad taste in the mouth, arteriosclerotic rigidity, and "Meniere's syndrome"[1084] Every consulting physician in this era of increasing geriatric practice and emphasis can attest to the frequency with which the evaluation of this consideration recurs in his daily differential diagnoses

The clinician must be ever cognizant of the potential for *cerebral embolization* in the patient with mitral stenosis who is doing well, particularly shortly after auricular fibrillation has begun This complication actually poses one of the great fears in delaying corrective cardiac surgery (p 479)

Particular emphasis should be directed to the variant syndromes of *cerebrovascular insufficiency* especially those stemming from involvement of the *basilar and carotid arterial systems* The striking liability that patients with this type of pathologic condition exhibit to the marked falls in blood pressure associated with changes in posture must be kept in mind when recurrent dizziness, vertigo, syncope, changes in vision, ataxia, dysarthria, and confusion ensue after such movements[1089] Under conditions of systemic hypotension or reduced cardiac output the collateral circulation of a brain whose arterial perfusion had already been previously compromised frequently becomes inadequate for its metabolic needs when the "critical closing pressure" is reached

The awareness and correct diagnosis of these syndromes is becoming increasingly important in view of the extensive use of powerful and potentially dangerous hypotensive drugs on the one hand and the beneficial effects of anticoagulant therapy on the other[1089b] In fact serious consequences can attend even relatively small drops in the blood pressure of patients with advanced arteriosclerotic disease of the carotid and basilar arteries The frequency with which this therapeutic implication might arise is underscored by the observation that neurologic signs and symptoms can be repeatedly induced in these patients when the minimal critical systolic pressure is reached—this level often being as high as 160 mm of mercury in certain hypertensive individuals[1090b]

The following situations in which remote disturbances of the heart and systemic circulation can create a state of reversible cerebral vascular insufficiency have been emphasized by Corday, Rothenberg and Weiner and are worthy of re-emphasis[1090a]

Hypotension due to hemorrhagic shock
Hypotension due to coronary shock
Hypotension due to the antihypertensive drugs
Postural hypotension (p 288)
Hypotension associated with the carotid sinus syndrome (p 293)
Hypotension due to other vasodepressor phenomena
Hypotension due to surgical procedures and anesthetics (p 432)
Postsympathectomy states
Cardiac arrhythmias
Pulmonary hypertension (p 275)
Congestive heart failure
Gravitational states

tively small (9 per cent in one series of 107 cases)[1096] One must note the considerable residual percentage of adult patients with seizures in whom no diagnosis can be made

The epileptogenic potential of cerebral cortical scars resulting from previous craniocerebral traumatic injuries merits added emphasis in this "jet" era[1096d]

A significant cause for seizures in later life is "degenerative" disease *of the brain leading to a diffuse atrophy with the histologic characteristics* of the amorphous cortical extracellular "senile plaques" and "Alzheimer's neurofibrillary change" within the nerve cells[1096b] *Alzheimer's disease* refers to these changes when they are accompanied by deterioration of the intellect in the presenile period *Pick's disease* presents much the same clinical features but is quite rare Pathologically, there is an unusual atrophy limited chiefly to the temporal or frontal lobes An even rarer degenerative encephalopathy occurring after the age of fifty is the *Jakob-Creutzfeldt disease* Clinically, it is characterized by focal and diffuse myoclonic jerks generalized convulsions, a rapid and profound dementia and death within one year from its onset

BRAIN TUMORS

A most embarrassing revelation common to all experienced psychiatrists is the finding of a brain tumor in patients thought to have psychosomatic disorders or psychoses, and who had been so treated[1097] A further disturbing fact is that in up to one half of the patients in many series of brain tumors there had been a delay in establishing the definitive diagnosis exceeding one year[1098] An analysis of these cases and of others in similar reports reveals the three main causes to be an inadequate neurologic history and examination false evaluation of the personality disorder, and a history of seizures not being explored further[1099]

Another relatively frequent set of circumstances under which the clinician s awareness of an underlying brain tumor is diminished occurs when the onset is apoplectic This is especially apt to be the case when remissions later take place[1100] The sudden onset of symptoms has been variously attributed to hemorrhage into the tumor compression of blood vessels by swelling of the tumor an acute block or shift of the ventricular system cerebral swelling and edema and secondary systemic factors relating to hydration, general nutrition electrolyte balance blood pressure changes, and alterations of cardiac function Consequently, if a "cerebrovascular accident" retrogresses but recurs more than once with the same signs and symptoms one should be alerted to the possibility of an intra cranial neoplasm Certain infiltrating neoplasms (especially oligodendrogliomas and slowly growing astrocytomas) may produce neuropsychiatric manifestations for as long as several years

Some of the pessimism concerning brain tumors is dispelled by the review of two large series recently presented by Grant and Horrax comprising 1603 and 1814 cases respectively[1101 110] In these reports it was clearly shown that approximately one out of three of these patients have a good chance for prolonged and useful activity following operation The

CONVULSIONS

In dealing with convulsions that have their onset after twenty years of age, experience in epilepsy clinics has shown that the di orders of a significant number of these patients will ultimately be found to have definite organic bases—even *after* an initial study by competent neurologists, neurosurgeons, and internists had failed to uncover the underlying brain tumor, metabolic disorder, or other neurologic and medical causes As a result of prolonged follow up studies in 689 such patients, the referring diagnosis of cryptogenic adult epilepsy was changed in one fourth of the cases The final diagnoses included brain tumor, brain abscess, cerebral birth trauma, psychogenic illness, pregnancy, neurosyphilis, cysticercosis, post-traumatic conditions, alcoholism, hypertension, and arteriosclerosis[1096a]

The term "epilepsy" can be particularly misleading when dealing with recent seizures in adults For example, the development of an acute organic mental state in women that is followed by rapidly progressive stupor and either focal or generalized convulsions—particularly during the first trimester of pregnancy—is often due to a spontaneous thrombosis of the superior longitudinal sinus[1038] Similarly, the administration of huge doses of penicillin intravenously (20 million or more units daily) can of itself produce convulsions A number of functional and biochemical derangements that might result in epileptiform attacks are recountered later in this chapter (p 369)

The occurrence of unexplained convulsions after several days in patients who are hospitalized for various conditions should immediately raise the possibility of a *withdrawal reaction* This no longer applies solely to the barbiturates and alcohol, but also to meprobamate and the other "tranquilizers[1164f] Because individuals who have become addicted to barbiturates, tranquilizers, or alcohol are also frequently subjected to head trauma, the clinician must not overlook the possibility of epidural or subdural bleeding and cerebral contusion when withdrawal convulsions are being considered, especially if focal convulsive activity is demonstrable

It is also important to regard the development of recurrent *convulsive seizures* for the first time *in patients over the age of forty years* in light of the statistical incidence of their various causes Such epileptiform seizures imply involvement of the cerebral cortex, most commonly in or near the classic motor and sensory areas Vascular diseases of the brain (cerebral infarction, cerebral embolism, sclerosis or thrombosis of the common or internal carotid artery) constitute the largest group (46 per cent in the Mayo Clinic s survey) followed in turn by traumatic lesions and degenerative disorders of the brain[1096b, c] Recurrent seizures may be the only clinical evidence of a previous cerebral cortical infarction The incidence of cerebral vascular lesions is stressed because these patients not only tolerate arteriography and pneumoencephalography poorly, but they may actually be made worse by such taxing examinations Accordingly, when the evidence points in this direction in an elderly patient, his best interests may be served by initially using conservative anticonvulsant therapy

Incidence of brain tumors as the cause of seizures in later life is rela

electroencephalographic and air studies (p 771) Poppen and Peacher have shown that the latter are not invariably reliable [1106] The clinician must be occasionally reminded of the great value of careful ophthalmoscopic and visual field studies (particularly in the presence of suspected parasellar tumors) (p 809),[1107] electroencephalography (p 773),[1108] routine chest films, and psychometric testing (p 773)[1082 1083] when an intracranial mass lesion is suspected

There are three common anomalies of the optic disc and retina which might possibly be mistaken for papilledema by those who are not familiar with these particular variants They include drusen bodies (which may cause an elevation of the disc surface), anomalous retinal vessels (which could simulate engorged veins), and medullated nerve fibers (which cause blurring of the disc margins) [1107c] Similarly, while the ophthalmoscopic appearance of early papilledema and that of a fully developed optic neuritis can be almost identical further observation will reveal both the unilateral nature and defective vision in the latter instance, along with the gradual regression of the edema of the optic disc over a period of several weeks [1107b]

The repeated and meticulous neurologic, spinal fluid and x-ray examinations under these circumstances may be most rewarding, even in very unusual brain tumors Several examples of the fruits of such diagnostic perseverance will be cited

1 The impairment of upward gaze is specifically related to pressure on the superior colliculus as can be produced by a *pinealoma* Patients with this tumor also have cells in the spinal fluid that resemble lymphocytes

2 The more frequent application of the stethoscope to the eyeball, the head and the orbit may on occasion be a valuable adjunct in the diagnosis of intracranial pathologic conditions [1109] For example, the finding of a *unilateral eyeball bruit* is highly suggestive of an occlusion and nar rowing affecting the cavernous portion of the internal carotid artery (One should be aware of the fact that the intracranial systolic bruit that is heard in some cases of occlusion of the internal carotid artery is most likely to be encountered on the side of the "good artery This is probably due to the increased rate of flow in this patent vessel and explains the otherwise paradoxical situation of an intracranial bruit being found on the same side as a hemiplegia)[1109d] It has also been noted in arteriovenous aneurysms, saccular aneurysms outer ridge meningiomas and other neoplastic conditions In these instances pressure on the ipsilateral common carotid artery will usually cause the bruit to disappear *Bilateral eyeball bruits* are encountered in hyperthyroidism and in severe anemia Since anemia is the most common cause of an intracranial bruit in a neurologically normal child the prognosis and diagnosis should be guarded when the hemoglobin is found to be normal [1109e]

3 Depression of the cribriform plate and enlargement of the internal auditory canal or erosion of the petrous apex may be highly indicative of *frontal and cerebellopontine angle tumors* respectively

4 Notching of the clivus is described as a specific radiographic sign associated with those *chordomas* which develop at the junction of the phenoid and occiput [109 1110]

meningiomas, acoustic neuromas, cerebellar and cerebral hemangiomas, astrocytomas, and craniopharyngiomas were particularly favorable lesions for excision In any statistical analysis of brain tumors, however, one can not fail to be impressed with the high incidence of metastatic disease (generally averaging 25 per cent) *which has its clinical onset in this fashion* (p 319)

A number of cases have been reported in which the clinical symptoms and signs of an expanding intracranial lesion were actually due to cerebrovascular disease with infarction and subsequent encephalomalacia [1103] Even the refined diagnostic x ray studies may support the clinical impression of a mass lesion, necessitating a craniotomy Vascular occlusions of the vertebral or cerebellar arteries, in particular, have simulated posterior fossa tumors, both clinically and radiographically The increased intracranial pressure so induced is presumably a result of the cerebellar or medullary softening, with concomitant compression and dislocation of the aqueduct and the fourth ventricle [1103b]

On the other hand, the diagnosis of an *intracerebral hematoma* is probably being made too frequently when that of a cerebral infarction would seem to be in order Neurosurgical intervention should usually be withheld until the complete syndrome appears to be developing This train of events consists of (1) a probable initial brain hemorrhage with coma or stupor, (2) restoration of consciousness in the presence of lateralizing neurologic signs, particularly the lateral shift of a calcified pineal gland, and (3) a subsequent loss of alert behavior associated with the manifestations of increasing intracranial pressure In the occasional patient with this picture evacuation of the clot has proved to be beneficial [1104]

One should distinguish between the distended, encapsulated, and fluid filled cavity *that remains after the clots have dissolved* and the more frequent situation in which there is a progressive breakdown of the blood clot, with a corresponding shrinkage in the artificial cavity that was produced by the original hemorrhage [1104c] Surgical intervention is obviously not indicated in the latter situation Pathologic studies have shown that the progressively enlarging intracerebral hematoma is most frequently located in the occipital, parietal, temporal, or frontal lobes (but rarely centrally) In all likelihood it results from either a direct communication *of the cyst with the ventricular system or the transfer of* fluid from the ventricle across the semipermeable ependymal lining of the cyst [1104c]

The so-called *Foster Kennedy syndrome* again demonstrates the tenet that there are very few signs in neurology (or in medicine) which are always pathognomonic This entity consists of a unilateral optic atrophy with papilledema in the opposite eye, and is usually associated with basofrontal tumors or abscesses of the brain It has also been noted, however, in sporadic cases of aneurysm of the internal carotid artery, arteriosclerosis and tortuosity *of the internal carotid and anterior cerebral* arteries, olfactory groove and cerebellar tumors arachnoiditis at the base of the brain, and in diabetes mellitus [1105]

It is of considerable interest that many brain tumors are diagnosed by finding significant abnormalities of the cerebrospinal fluid than are revealed with the other technical diagnostic aids employed, including

blood constituent In some instances ammonium chloride appeared to aggravate the movement disorder, even though there had been an improvement in the oxygen saturation and a reduction in the carbon dioxide tension

"HYDROCEPHALIC CRISES"

The occurrence of transient episodes of severe headache, dimness of vision bilaterally, roaring in the ears a curious generalized numb sensation and occasionally the loss of consciousness are suggestive of "hydrocephalic crises ' This syndrome is characteristically noted in situations wherein there is an intermittent obstruction to the cerebrospinal fluid flow, either at the interventricular foramina the aqueduct of Sylvius, or at the foramina for the exit of the spinal fluid from either the fourth ventricle or the basal cisterns [1115]

SUBDURAL HEMATOMA

One cannot conclude this theme without reference to the subject of subdural hematoma—all the more important because this is usually a remediable condition *if* diagnosed in time Even with careful questioning in retrospect, a history of trauma to the skull often cannot be elicited The clinical findings may be so protean as to suggest a brain tumor, a cerebrovascular accident, an encephalopathy due to other causes a psychosis or possibly a meningitis if a high spinal leukocyte count happens to be present [1113] On the basis of a suspicious history of head trauma behavioral peculiarities and inequality of the pupils burr holes should be very seriously contemplated, even when all the other studies are non revealing or inconclusive

In their review of 30 000 patients with trauma to the head, Echlin and his colleagues found operable subdural hematomas in about 1 per cent [1114] They stress the importance of appreciating the existence of not only the acute and chronic groups, but of the larger subacute group of cases who exhibit unexplained progressive mental or neurologic phenomena seven to twenty one days after the injury The presence of a marked pupillary dilatation on one side along with the drifting of one of the outstretched arms may be early valuable clues One should not be too dogmatic about localizing signs, however, in view of the significant frequency with which bilateral hematomas occur Inasmuch as approximately 20 per cent of chronic subdural hematomas are bilateral, a displaced pineal gland might not be a completely conclusive sign

A clinically significant subdural hematoma occasionally complicates the intracranial bleeding stemming from a ruptured intracranial aneurysm the surgical treatment of which could possibly be life-saving [1113b] Notwithstanding the aid of arteriography this complication may still be difficult to recognize

A *subdural hygroma* (or subdural hydroma) infrequently follows trauma to the head It results from a small tear in the arachnoid which permits the escape of some spinal fluid into the subdural space The fluid may be xanthochromic and high in its protein content With the ensuing accumula

OTHER DISORDERS RESULTING IN INCREASED INTRACRANIAL PRESSURE OR SIMULATING BRAIN TUMORS

Pseudotumor Cerebri and Emphysematous Encephalopathy

It is proper to also focus some attention on *pseudotumor cerebri* because most clinicians are not familiar with this entity and its relatively good prognosis [1111] The author has encountered several patients with this disorder who had been misdiagnosed even by eminent neurologists and neurosurgeons, in fact, all were subjected to surgical exploration and decompression procedures This condition is characterized by the usual signs of increased intracranial pressure (elevated cerebrospinal fluid pressure, headache, vomiting, papilledema), absent or minimal abnormal neurologic signs (a lateral rectus palsy and diplopia are the most frequent ones encountered), normal spinal fluid, and a normal or small ventricular system shown by pneumoventriculography

The disorder is apparently due to transient vasomotor changes and an associated cerebral edema It has been the general experience that the greatest frequency of this disease is among women under the age of thirty Pseudotumor cerebri may exhibit a dramatic response to a conservative regimen of fluid and salt restriction (but without decompression) If a tumor is actually responsible for the presenting picture, it will almost always be clinically demonstrable within one year

The occurrence of papilledema and a high cerebrospinal fluid pressure has been described in association with pulmonary emphysema This phenomenon is attributed to the effect of the elevated carbon dioxide levels on the intracranial vasculature and to the increased viscosity of the blood resulting from the secondary polycythemia [1112] Alleviation of the papilledema has followed elimination of the respiratory acidosis Other features resulting from the hypercapnia and acidosis that might lead to an erroneous diagnosis of brain tumor include progressively severe headaches, personality changes, somnolence, confusion, coma, retinal hemorrhages, syncopal episodes, abnormal pupillary reflexes, and even localized paralyses These cases of "*emphysematous encephalopathy*" may closely simulate intracranial hypertension of unknown cause (pseudotumor cerebri)

It is of interest that some of these patients have apparently experienced considerable relief from their headaches and mental symptoms by the ingestion of large amounts of aspirin Such a response might be explained by the known fact that the salicylates can induce periodic hyperventilation through their direct respiratory stimulant action thus reducing the carbon dioxide tension level The maintenance of the carbon dioxide sensitivity of the respiratory center achieved in this manner allows for both the establishment of a gradually progressive respiratory acidosis and a sufficiently long period of time for papilledema to result from the concomitantly increased intracranial pressure

Included among the neurologic complications of pulmonary insufficiency are twitching and tremors which for all practical purposes simulate those encountered in hepatic coma [111c] In some (but not all) of these individuals, the blood ammonia is somewhat elevated, although no correlation could be demonstrated between the severity of the twitching and this

sociation of aneurysms of the cerebral vessels with polycystic disease of the kidneys and liver will be further emphasized under Group XIV (p 422) The generalized pigmentation associated with many types of intracranial disea e will be cited under Group XVII (p 515) The frequent psychiatric manifestations in certain organic illnesses (most notably hyperinsulinism, carcinoma of the pancreas, hypothyroidism, brucellosis, and porphyria) were alluded to earlier in this chapter

Certain *functional and biochemical derangements* which have been men tioned *as causes of convulsions and coma* bear repeated emphasis These include water intoxication (p 477), uremia (p 50) ammonia intoxication (p 97), carotid sinus hypersensitivity (p 293) Stokes-Adams seizures hypoparathyroidism (p 27), other causes for hypocalcemia, hyperinsulin ism (p 19), other causes for hypoglycemia severe anemia or blood loss, angioneurotic edema, withdrawal syndromes in addicts (p 362), and ad renal insufficiency (p 13)

The neuropsychiatric features of *hepatic insufficiency* have received much attention in recent years, particularly with the increased emphasis on derangements of ammonia metabolism Fluctuating mental disorders with confusion disorientation bizarre behavior, and recurrent coma may be associated with such striking objective signs as a "flapping tremor, hyperreflexia, and limb rigidity [350 354] While there can be little doubt that the flapping tremor' is most characteristic of severe liver disease it has been encountered in patients with uremia (in the absence of demonstrable liver disease) polycythemia vera, severe malnutrition, pulmonary insuffi ciency [111] and steatorrhea [356]

Even within the realms of mental deficiency and psychiatric illness, it is becoming increa ingly important to be aware of certain underlying bio chemical derangements for prophylactic and therapeutic reasons This con sideration has already been alluded to in the discussion of *congenital galac tosemia* a condition in which it is possible to prevent mental retardation by the earliest institution of a galactose-free diet (p 75) [275]

In this same regard a number of observers have shown the remarkable improvement in the behavior of patients with *phenylpyruvic oligophrenia* when a phenylalanine-restricted diet is instituted for extended periods [1117] It has also been demonstrated that this type of a dietary regimen may prevent motor and mental abnormalities in the newborn siblings of such patients *if* it is begun shortly after the urinary ferric chloride test becomes positive This hereditary defect in phenylalanine-tyrosine metabolism has a tendency to affect individuals with fair hair blue eyes and a blond complexion Convulsive seizures, dermatitis and a musty odor are other features of this disorder A presumptive diagnosis of phenylpyruvic oligophrenia can be made with considerable accuracy in children having mental deficiency by the characteristic dark bluish green color that develops when ferric chloride solution is added to acidified urine

MYASTHENIA GRAVIS

In the early phases of assembling this bool the author deliberated at great length as to whether myasthenia gravis actually poses the problem

tion of fluid, evidence for a space occupying lesion is found especially in the form of headaches and lateralizing signs The prognosis is usually good following evacuation[1114b]

The potential complications following surgical removal of a subdural hematoma will be set forth in a later chapter (p 482)

Cysticercosis Cerebri

Reference was made in an earlier chapter to the increasing importance in the neurosurgical centers of this country of cysticercosis cerebri (p 175) This condition results from infection of the human brain by the larval form of *Taenia solium* The less severe form of this disease, consisting of solitary cysts, can readily simulate the manifestations of the more common types of brain tumors In several instances an obstructive hydrocephalus was incorrectly attributed to a midline tumor in the posterior fossa[633]

This diagnosis merits serious consideration when features attributable to an expanding intracranial mass occur in individuals who have long resided in such countries as Mexico, Chile, and Spain It is even more suggestive when they are associated with multiple small areas of intracranial calcification, an eosinophilia of the blood and spinal fluid, and a positive complement fixation test of the spinal fluid to an alcoholic extract of porcine cysticerci (p 742)

CENTRAL NERVOUS SYSTEM MANIFESTATIONS OF SYSTEMIC DISEASE

Manifestations in the central nervous system are frequently the first indications of serious infection sepsis, or toxicity from many diverse causes This is particularly true of '*acute brain purpura*' or pericapillary encephalorrhagia This condition is characterized by tiny sharply circumscribed foci of pericapillary or perivenular necrosis occurring primarily in the white matter but with no vascular occlusions[1116] The clinical picture is manifested by clouding of the consciousness (even to the degree of coma) and convulsions but without focal neurologic signs or changes in the spinal fluid When resulting from an underlying septicemia it is usually misdiagnosed as representing multiple septic emboli to the brain

Reference is again made to the significant *neurologic and myopathic components of many systemic disorders* which have been mentioned throughout this book These include the cardiac manifestations of myotonia dystrophica (p 422) and Friedreich s ataxia (p 268), the association of thymic tumors with myasthenia gravis (p 371) the myasthenic syndrome associated with certain malignant neoplasms (p 323) the periodic paralysis associated with thyrotoxicosis (p 18) the increased incidence of pulmonary changes along with tumors of the heart and kidneys in tuberous sclerosis (p 426), and the hepatolenticular degeneration in Wilson s disease (p 100) In other sections the neurologic manifestations of fat embolism (p 217), thrombohemolytic thrombocytopenic purpura (p 218) porphyria (p 61) the various poisonings (p 64), the endocrinopathies endocarditis (p 114), the granulomata, and the collagen diseases are discussed The frequent as

fully opened at will and the sense of fatigue quickly overcome by both proper motivation and enthusiasm this is not possible in the case of the myasthenic individual (whose muscles are in a sense paralyzed rather than weak) and (3) the clinical response to cholinergic therapy True myasthenia is unlikely if side effects occur before clinical improvement is noted when the cholinergic agents are given Even if improvement follows the oral ingestion of Mestinon or another cholinergic drug it is wise to obtain a confirmatory intravenous test The most specific of all the tests—the response to which cannot be influenced by either motivational factors or suggestibility—involves the electrical stimulation of a motor nerve and the objective recording of the induced muscular contraction on a ergogram or an electromyogram In such studies the motor performance of the patient with true myasthenia is markedly enhanced by the administration of a cholinergic drug This contrasts with the absence of such a response in the fatigued individual

While much still remains to be learned about the deranged physiology of neuromuscular transmission in myasthenia gravis it appears that events proceed normally through the stage of production of choline by the hydrolysis of acetylcholine The choline so released however, produces a competitive type of block in the myasthenia end plate membrane This in turn inhibits the depolarizing action of the acetylcholine that is released by subsequent nerve impulses [1118b]

The striking incidence of associated thymic tumors in myasthenia gravis is noteworthy The extensive experiences of Eaton and Clagett at the Mayo Clinic and of Schwab and Leland at the Massachusetts General Hospital pertaining to the performance of a thymectomy in the treatment of myasthenia gravis indicate that this procedure is of the greatest benefit to female myasthenic patients who are less than fifty years of age and who do *not* have thymomas [1118 d] This is not true however when the disease has been present for more than ten years and has remained relatively stationary Patients who experience exacerbations of their myasthenia during the menstrual periods and remissions during pregnancies appear to achieve satisfactory results after a thymectomy more frequently One should also be aware of the fact that there are approximately 10 cases described to date in which myasthenia gravis appeared for the first time *following* the removal of a thymoma [1118g]

Several comments are in order concerning the use of the term *crisis* as applied to myasthenia gravis It would appear that two types should be distinguished because of the profound differences in the indicated therapy The true myasthenic crisis occurs in those patients who have received little or no medication or in whom drug resistance develops On the other hand the cholinergic crisis results from excessive medication In this regard attention is directed to the unwise practice in some quarters of prescribing a belladonna alkaloid along with oral neostigmine In so doing one runs the risk of masking important side effects and allowing excessive amounts of the drug to be taken [1118h] The pharmacologic differentiation of these crises is described in other sections (pp 480 and 811)

Anesthetists should be aware of the possibility that a crisis might be precipitated in the unsuspected myasthenic individual by the administra

of puzzling illness often enough to merit its inclusion His experience over the ensuing years has pointed out in striking manner the frequency with which this entity must be considered

On the one hand, many neurologic pictures can be simulated Among these, mention is specifically made of isolated cranial nerve palsies, multiple sclerosis, the other "degenerative" disorders of the central nervous system, and bulbar paralysis due to neoplasms, infections (particularly poliomyelitis and infectious polyneuritis), and vascular occlusions Furthermore, since myasthenia gravis can affect almost any striated muscle in the body, it may be confused with the severe weakness that characterizes hyperthyroidism and periodic familial paralysis This disorder is at times mimicked by the patient with hysteria On the other hand, many patients with mild myasthenia have carried the label of "psychoneurosis" for years until the true diagnosis was made Unfortunately, a false-positive response to certain of the therapeutic diagnostic tests has occurred in the latter group—even with Tensilon—so that it is often necessary to employ placebos in this pharmacologic differentiation

There is usually little difficulty encountered in recognizing the severe or typical case of true myasthenia gravis Mild cases of this disorder can be readily overlooked, however, when the condition is not progressive, in the patient who is not incapacitated, and wherein the ptosis, constipation, slurring of speech, and dyspnea are slight [1118a] Fatigue and aching of the neck, back, arms, and legs are apt to characterize this less severe form of the disease Since there is usually sufficient reserve strength available in muscles of the limbs, the myasthenic patient often remains relatively active provided his weakness is not brought on by the excessive climbing of stairs or lifting The symptoms are also aggravated by infection and emotional upsets Spontaneous exacerbations and remissions are common in this disease, and have occurred in up to one fifth of the case series reported

The diagnosis of myasthenia should be made with great reservation in these atypical cases until an unequivocally positive response is forthcoming to the various pharmacologic and therapeutic tests for this condition (p 811) The characteristic posture and facies of the myasthenic patient must be sharply distinguished from that of the excessively tired individual with sleepy, half closed eyes The importance of regarding myasthenia as a possible manifestation of a concomitant malignant tumor (particularly small cell carcinomas of the lung) and the value of electromyographic study in this differentiation are cited elsewhere (pp 323 and 774) The reader is also referred to a previous chapter for a discussion of the interesting relationship between thyrotoxicosis and myasthenia gravis (p 16)

There are three highly important clinical criteria that can aid the clinician in differentiating a patient with this disorder from the fatigued individual (who often first presents himself after reading a description of the disease in a health column in some newspaper or magazine) These include the following (1) whereas true myasthenia is improved by rest—and accordingly is better in the morning—the usual chronic nervous exhaustion is apt to be most bothersome on awakening and then improves with activity, (2) whereas the sleepy eyes of the tired individual can be

countered in diagnosing the advanced case, clinicians should be aware of the following considerations which may prove to be confusing in some of the early or atypical instances of this disorder [1119]

1 Muscular cramping and weakness may be the presenting symptoms The occasional patient with this disease who complains of increasing muscular weakness with fatigue may even exhibit a myasthenic type of response to the use of prostigmine

2 Since the weakness and atrophy of the muscles may remain confined to one hand for as long as a year these manifestations should not be confused with such peripheral nerve lesions as a median thenar neuritis or a bilateral tardy ulnar palsy The characteristic innervation pattern and sensory involvement in the latter instances can preclude this error

3 A significant number of these patients will first experience their muscular weakness in the lower limbs Since the anterior tibial and gastrocnemius muscles are usually affected a flail foot might develop

4 Should the pyramidal tracts be involved at or above the level of the brain stem there may be evidences of a pseudobulbar palsy It is interesting to note that brisk abdominal reflexes may be found in the presence of positive Babinski responses in some of these patients, and that involvement of the extraocular muscles and the bladder sphincters is rather infrequent

5 The possibility of compression of the spinal cord by some extradural lesion (i e disc, tumor hypertrophic ridging of the cervical spine) must always be entertained when the muscular weakness atrophy and fasciculations are limited to several segments The importance of careful myelographic studies being carried out—even to the level of the foramen magnum—is cited elsewhere in this chapter (p 376)

6 A chronic neuronopathy may be most atypical and could simulate amyotrophic lateral sclerosis very closely when the motor involvement is profound and the sensory component minimal Atrophy and fasciculations might occur Differentiation by spinal fluid studies and electromyography is highly important in view of the favorable prognosis of most neuronopathies

7 The Charcot Marie Tooth syndrome progressive familial spastic paraplegia and certain other of the heredodegenerative disorders of the nervous system which might be confused with this disease develop at a much earlier age and exhibit more benign courses as a rule

8 A puzzling exertional dyspnea may be experienced early in the course of the disease when the process chiefly affects the muscles of respiration

SYNDROMES DUE TO INVOLVEMENT OF THE HYPOTHALAMUS AND THIRD VENTRICLE

It is apparent to all who would consider the physiologic importance i the body s economy of the nerve centers found in and around the hypoialamus and third ventricle that disease in this small but intensely vital 'ea may affect many systems Nonetheless such a consideration is rarely icountered in everyday diagnostics Bauer has made a study of this prob-

tion of the curare like drugs for surgical and other purposes (p 480) An adequate airway must first be insured in the patient with myasthenia who has difficulty either in breathing or expectorating The use of a tracheotomy and a respirator should not be delayed too long under these circumstances

There are many possible patterns of symptomatology in the case of the woman with myasthenia gravis who becomes pregnant These responses usually become evident during the first trimester In a study of 33 such pregnancies in 22 patients, Osserman noted that one third of the patients exhibited a definite remission, one third showed no change in symptoms, and one third had a definite relapse [1118f] It is interesting that the patterns of the myasthenia during subsequent pregnancies need not necessarily follow those of a previous gestation

AMYOTROPHIC LATERAL SCLEROSIS

While no detailed discussion of the various muscular dystrophies and atrophies will be attempted in this book, amyotrophic lateral sclerosis deserves some mention for the following four reasons (1) it is not rare, (2) the disorder may be localized to an extremity for a long period of time, during which time accurate diagnosis is possible by electromyography (p 774), (3) the early or atypical case might offer considerable difficulties in diagnosis, and (4) the disorder may occasionally have important hereditary aspects With reference to incidence, it is pointed out that approximately 100 new cases are seen annually at the Mayo Clinic, this frequency representing twice that of myasthenia gravis and one third that of multiple sclerosis as encountered at that institution [1119]

This disorder is a motor system affliction occurring in adult life that is characterized clinically by a progressive muscular atrophy (which may begin anywhere in the skeletal musculature), fasciculations, the manifestations of pyramidal tract involvement, and an eventually fatal course The various terminologies applied to the many variants of this entity have at times confused the subject for clinicians who have no intimate contact with neurological practice These include the amyotrophic lateral sclerosis of Charcot, the progressive muscular atrophy of Aran Duchenne, and progressive bulbar palsy

In addition to the involvement of the skeletal muscles, pathological studies have demonstrated impairment of the visceral musculature of the urinary bladder, the gastrointestinal tract, the esophagus and the myocardium In all 19 patients with this disease whose esophageal motility was studied by Smith, Mulder and Code, diminished peristaltic pressures or an incoordinate peristaltic activity were observed in all [1119] (This derangement may also be due in part to the destruction of the dorsal motor nucleus of the tenth nerve) The tachycardia in some of these patients has been attributed to the autonomic nervous system involvement

All texts on neurology present excellent descriptions of the advanced clinical picture of amyotrophic lateral sclerosis particularly with reference to the features of the muscular atrophy, the bulbar palsy, the pseudobulbar palsy and the lateral sclerosis Although there is little difficulty en

to the widespread use of vitamin supplements containing folic acid has been cited under Group VI (p 191) Since the progress of subacute combined sclerosis can be permanently arrested in *every* case by adequate parenteral therapy, an increase or a recurrence of neurologic signs and symptoms on such a regimen warrants the careful search for a coexisting spinal cord tumor [11 15]

2 It would appear paradoxic in this antibiotic era to emphasize the fact that the lesions of *meningovascular and tertiary syphilis* can simulate *any and all* types of pathologic conditions of the spinal cord It is an unfortunate fact however, that the present generations of physicians will have to be imbued with this aphorism which was so well appreciated by physicians in previous decades This point was clearly demonstrated in a recent report of a long term follow up program among veterans of World War II who had acquired syphilis [55] Should the diagnosis still be questionable after the initial studies have been carried out, an adequate course of penicillin may serve as a good diagnostic therapeutic test (p 814) Fortunately when doubt exists the finding of either a positive serology or a positive *Treponema pallidum* immobilizing test in the spinal fluid is diagnostically conclusive (p 155) [555]

3 The myelopathy due to a number of *metabolic and infectious polyneuropathies* that are subsequently listed in this chapter (particularly diabetes mellitus and trichinosis) can be checked or reversed by adequate therapy The granulomata of tuberculosis actinomycosis and (in certain endemic areas) the lesions of schistosomiasis and other parasitic diseases may also exert pressure on the spinal cord [631]

Neurologic involvement of the spinal cord or the spinal roots in a patient with diabetes mellitus does *not* automatically justify the diagnosis of a diabetic neuropathy unless an attempt has been made to exclude other disorders involving these structures [58c] The spinal fluid protein is often elevated in a diabetic neuropathy Neither the severity nor the control of the patient s diabetes is in itself a reliable criterion in establishing or excluding this complication

4 The importance of considering the diagnosis of a *herniated intervertebral disc* in the presence of neurologic changes that affect the extremities and which involve sensation, motor power or reflexes is at once apparent The clinical variations are numerous and at times confusing This is particularly true in the presence of discs at multiple levels or when negative myelograms are obtained Unilateral sciatic pain a low backache with a positive Lasèque sign or sciatic nerve tenderness may be the only demonstrable clinical features of a lumbar disc [112]

All orthopedists and neurosurgeons can attest to the difficulties in separating this disorder from the low backache and sciatic pain of intraspinal tumors structural vertebral anomalies in the lumbosacral area the pelvis or the hip joint prostatic or gynecologic disturbances rheumatoid spondylitis and malingering More specifically one should include osteoid osteoma and various tumors of the femur twisted ovarian cysts multiple myeloma Paget s disease of bone eosinophilic granuloma of the pelvis pelvic neoplasms herniation of the subfascial fat and a short leg [11-3]

It is equally imperative to appreciate the fact that compression of the

lem in 60 autopsied patients with neoplastic, inflammatory, and degenerative lesions affecting these structures[1120] He found that the average number of hypothalamic linked symptoms was three These included modification of sexual function and development, growth disturbances, diabetes insipidus, sleep and psychic changes, obesity or emaciation, elevated or subnormal temperatures, neuro-ophthalmologic aberrations, and abnormal intermediary metabolism It was of great interest that there was no definite correlation between the extent of involvement and the degree of functional disability Lesions involving the floor of the third ventricle appeared to manifest more symptoms than those involving either the walls or the roof

Several reports have stressed the significant hypernatremia and hyperchloremia secondary to lesions or operations in the region of the hypothalamus and third ventricle,[309] and the sodium-losing syndromes associated with certain central nervous system tumors (p 82) In a previous chapter dealing with obscure fever, reference was made to the importance of considering hypothalamic disorders when an unexplained elevated body temperature persisted in the face of a relatively normal pulse, white blood cell count, and sedimentation rate (p 105) The "coma vigil" in hypothalamic syndromes is quite unique It is often accompanied, on the one hand, by marked pallor, fever, sweating, and changes in the pulse and blood pressure, but with a paucity of brain stem signs and paralysis on the other In certain instances, seizures originating from this area have responded to a stimulant, such as ephedrine, when the sedative drugs had no effect While the development of excessive sexual urge is a striking manifestation of hypothalamic lesions, one must also be aware of the ability of certain brain tumors (especially those in the frontal lobe or parasagittal areas) to present in this manner

POTENTIALLY TREATABLE SPINAL CORD DISORDERS

The subject of potentially treatable spinal cord disorders is so important to the welfare of the patients afflicted in this manner—particularly in view of the frequency with which the underlying diagnoses may be delayed or completely missed—that further amplification is mandatory in a text of this type The necessity for a detailed description of the pain, weakness or sensory levels, the relationship of the symptoms to factors that might result in elevation of the spinal fluid pressure, and careful, complete spinal fluid studies (dynamics, protein content, xanthochromia) is obvious[11 14] Attention will be directed to fourteen types of remediable spinal cord lesions which the author has frequently been required to consider in the evaluation of undiagnosed spinal cord and peripheral nerve phenomena

1 *Combined system disease* due to vitamin B_{12} deficiency must always be kept in mind when atypical cord dysfunction affects the older age groups The simultaneous occurrence of symmetric numbness and paresthesias in all four extremities the absence of Achilles tendon reflexes, and the presence of a positive Babinski sign can only rarely be produced by cervical intraspinal tumors If any doubt exists an intensive trial on vitamin B_{12} therapy is always indicated even in the absence of a significant anemia The apparent increasing incidence of this disorder, related in part

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The ımportance of consıderıng the dıagnosıs of a *hernıated ınter ' dısc* ın the presence of neurologıc changes that affect the extrem d whıch ınvolve sensatıon motor power or reflexes ıs at once ap- The clınıcal varıatıons are numerous and at tımes confusıng Thıs ıularly true ın the presence of dıscs at multıple levels or when 'nega- ıyelograms are obtaıned Unılateral scıatıc paın, a low backache posıtıve Lasèque sıgn or scıatıc nerve tenderness may be the only trable clınıcal features of a lumbar dısc [11 2]

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ıs equally ımperatıve to apprecıate the fact that compressıon of the

cervical spinal cord by a herniated disc may closely simulate such degenerative diseases of the spinal cord as multiple sclerosis (p 357) and amyotrophic lateral sclerosis (p 373) Furthermore, the radiation of the pain in this condition has on occasion closely simulated that of angina pectoris [868b]

5 Unsuspected *traumatic lesions of the cord* may be due to compression fractures resulting from osteoporosis, malignancy, or manipulation The underlying abnormality can usually be ascertained by careful x ray studies The very high incidence of functional symptoms in cases of "whiplash" injuries to the neck during pending litigation or compensation claims must also be borne in mind [1130]

The injury to the spinal cord may be more subtle, however, as in the case of the compression syndromes due to *Paget s disease of bone*[1124] or to *spondylosis of the cervical vertebrae* [1125a] The latter condition is apt to produce repeated minor traumata to the cord during flexion extension movements of the neck A variety of ensuing subjective and objective neurologic disturbances in the upper and lower limbs has been described A conservative operation (usually consisting of a laminectomy with section of the dentate ligament) should be reserved for the patient in whom the symptoms are recent and rapidly progressive [1125a] One interesting case report has appeared in which the Paget's disease was localized at the axis and produced a quadriplegia [1124b]

6 *Tumors of the spinal cord* must be seriously considered and the diagnosis actively pursued in *every* atypical case diagnosed as either a herniated disc, combined system disease, or "degenerative disease" of the spinal cord One should favor this diagnosis over that of a herniated disc in the presence of bilateral sciatic pain, nocturnal pain loss of both vesical and rectal sphincter control, and marked sensory loss with atrophy of the muscles in the lower extremities [1126] Space occupying lesions lying anterior to the spinal cord are particularly prone to produce primarily motor symptoms, without sensory alterations Although many exceptions have been noted, an absent ankle jerk usually indicates a lesion at the fourth or fifth lumbar interspace, whereas an absent knee jerk suggests a lesion at or above the third interspace Conus lesions can also produce absent ankle or knee jerks but not a positive Babinski sign

Scott has pointed out that tumors involving the high thoracic cord (and even the cervical cord) can occasionally produce lower extremity pain simulating sciatica, and in so doing tend to obscure the true level of the lesion [1126d] The diagnoses that might be made in such a situation may range from incomplete peripheral nerve lesions to vascular disease, herniated discs, and thalamic lesions It is stressed that a "burning" quality of pain in the lower limbs should direct one s attention to a spinal cord disorder If the lumbar myelogram is either negative or equivocal in this situation, the contrast medium should be run through the entire thoracic canal

The possibility of a spinal cord tumor must be given added thought in the case of a patient over thirty five years of age who appears to develop multiple sclerosis, or in the case of a child or young adult who exhibits features suggestive of amyotrophic lateral sclerosis [1127] In the presence of posterior cervical pain, cervico-occipital headaches, nuchal stiffne s bizarre neurologic symptoms, and motor sensory reflex evidence suggestive of "de-

generative disease of the nervous system, a benign extramedullary tumor arising at the level of the foramen magnum should be considered [1123] The finding of an enlargement of the foramen between the first and second cervical vertebrae is also highly suggestive of this diagnosis

The clinical heralding of these lesions by herpes zoster should be borne in mind when this infection suddenly asserts itself (p 523) Similarly, an unexplained pain in the chest, abdomen, back or the extremities which is aggravated by rises of the intraspinal pressure incident to coughing, sneezing or straining should suggest either a true spinal cord tumor, or impingement onto the cord and its roots by a lymphoma or myeloma Craig has presented a large series of patients with intraspinal tumors in whom the pain syndrome simulated diseases of the pericardium and the pleura, diseases of the biliary, urinary, and gastrointestinal tracts and diseases of the peripheral nerves muscles and bones [11 6]

The importance of seeking out cafe au lait spots and neurofibromas of the skin and peripheral nerves in von Recklinghausen s disease is apparent It is of interest that various non neoplastic disorders such as amyloid deposits may behave in a similar manner The rapid onset of a diplegia following lumbar puncture is also suggestive of a spinal cord tumor The clinician should be aware of the fact that the early symptoms of a para sagittal brain tumor can resemble those of a spinal cord tumor

Chordomas are mentioned as unusual tumors that may involve any segment of the spinal axis, although the great majority arise either in the basioccipital or sacrococcygeal regions [1110] They are usually characterized by slow expansile growth with destruction of bone and extension to adjacent structures so that an extraosseous soft tissue component is almost a constant finding The clinical onset is very insidious and often evolves over a period of years rather than months There are no pathognomonic fea tures however so that the lesion is commonly diagnosed as a primary intraspinal tumor metastases a herniated disc, a presacral teratoma or cyst simple backache, and giant cell tumor Chordomas can also be readily confused with a chronic inflammatory disease particularly tuberculosis [1110c] The preservation of the intervertebral spaces and the adjacent soft tissue mass, with or without calcification should point away from this particular infectious causation (but does not exclude other rarer infections such as actinomycosis and blastomycosis)

Almost all the cranial chordomas arise from the region of the spheno-occipital synchondrosis (p 365) A correct preoperative diagnosis of the sacrococcygeal tumor can be arrived at on the basis of a lobulated midline osteolytic defect with well defined margins a marked soft tissue mass and a prolonged clinical course It is of interest that chordomas hardly ever arise from the residual notochordal tissue found in the intervertebral disc

The many considerations relative to the roentgenographic diagnosis of spinal tumors both with and without the use of contrast media have been well reviewed in several recent reports [11 6c] The appearance of and the distance between the pedicles of the spine are particularly important to study It is rare for these tumors to cause collapse of the adjacent vertebrae by invasion of bone In such instances, tuberculosis brucellosis and pri mary or metastatic malignancy of the vertebrae merit careful considera

tion Most of the extradural spinal tumors are malignant and arise from structures outside the dura, while the majority of the intradural tumors arise from the spinal cord (intramedullary) or the nerve roots and meninges (extramedullary) Detailed myelographic studies with ample views should be carried out sufficiently high in the lumbar and lower thoracic areas, since a certain percentage of spinal tumors are multiple (as is also the case with herniated discs)

7 Cord compression due to *myeloma* is not infrequently encountered (this being the presenting feature in 8 of 57 cases in one series) It may produce complete paralysis of the lower extremities rather rapidly The *underlying pathologic condition may be due to an extramedullary tumor*, a collapsed vertebra, or a perineural myelomatous invasion Complete restoration of function can be achieved by laminectomy, cord decompression, and drug therapy [671, 672]

8 The problem of *radiation myelitis* as it may affect the entire spinal axis is discussed in greater detail under Group XIII (p 400) While not actually a treatable myelopathy, it can usually be prevented by the therapist not exceeding the radiation tolerance limit of the central nervous system (3500 to 4500r) [1 04]

9 *Nontuberculous spinal epidural infection* is an entity representing a true surgical emergency that is infrequently even suspected prior to the occurrence of severe damage The infection is usually due to the dissemination of *Staphylococcus aureus* from various chronic foci of infection, including acne, furunculosis, cellulitis, vertebral caries, and old operative sites The tragic suddenness of the irreversible neurologic damage can be averted by an accurate diagnosis in the preparalytic phase Heusner has classified the various syndromes as follows acute spinal epidural infections (including the metastatic and osteomyelitic forms) and chronic spinal epidural infections (including the metastatic and osteomyelitic forms) [471] *In addition* to the epiphenomena of unrestrained sepsis, there is a basic clinical pattern common to all the variants, represented by the following train of events

Phase 1 Spinal ache
Phase 2 Root pain
Phase 3 Weakness of the voluntary muscles, sphincters, and sensibilities
Phase 4 Paralyses

Characteristically, one encounters a total or subtotal subarachnoid block of the spinal fluid circulation in all these syndromes, but *no* chemical or bacteriologic evidence of leptomeningitis (While the procedure of lumbar puncture probably carries some risk—even when properly performed very carefully—it may be of crucial importance to early diagnosis) *Spinal* epidural infections are almost always initially diagnosed as meningitis, poliomyelitis, infectious polyneuritis rheumatoid arthritis, tuberculous spondylitis, perinephric abscess or neurosis A fine review of the roentgen manifestations of these epidural granulomas has been presented by Campbell and Silver [1129]

10 It is well to bear in mind the diagnosis of a *dissecting aortic aneurysm* in the hypertensive patient who exhibits changes suggestive of an acute arterial occlusion of the spinal cord [895]

11 While admittedly uncommon, the occurrence of serious *neurologic complications following spinal anesthesia* must be considered when spinal cord symptoms persist following this procedure Radiculitis, the cauda equina syndrome, ascending myelitis, adhesive arachnoiditis meningitis, and meningoencephalitis have all been reported [1131] The spinal fluid studies, irrigation of the subarachnoid space, institution of tidal drainage of the urinary bladder, and care of the bowels as outlined by Nicholson and Eversole should be considered in the patient exhibiting a delay in the return of motor and sensory function [113] Spinal anesthesia can also precipitate certain pre-existing neurologic conditions These include multiple sclerosis combined system disease, spinal cord tumor, cerebrovascular disease and its complications, central nervous system syphilis, amyotrophic lateral sclerosis progressive muscular atrophy, and diabetic neuropathy [1133]

12 Several reports of a *spinal cord extradural hematoma* occurring during the course of anticoagulant therapy have appeared [1134] If a paraplegia is to be averted, this diagnosis must be actively pursued by myelographic studies (after counteracting the hypoprothrombinemic state) when patients receiving these drugs complain of recent low back or sciatic pain, along with early numbness or weakness of the legs Extradural hematomas have also been encountered in vertebral fractures, leukemia, hemophilia and toxic febrile illnesses

13 *Decompression sickness* occurring in "skin divers" who have not been instructed as to the hazards of this sport can simulate an infectious myelitis or a Guillain Barré syndrome If the attending physician is not alerted to this diagnosis and procrastinates unduly before instituting recompression and proper stage recompression therapy permanent spinal cord destruction or death can ensue (p 217) [796f] Bubble formation is more prone to take place in the spinal cord than in the brain because of the longer saturation desaturation time of nitrogen there

14 The development of neurologic symptoms and signs referable to spinal cord involvement in the patient with myelophthisic anemia and myeloid metaplasia may be caused by compression of the cord by *extra medullary hematopoiesis* in the extradural space rather than the blood dyscrasia itself [1134b] Radiation must obviously be used judiciously in such an instance in order to prevent the possible destruction of vital hematopoietic elements in the liver and spleen

THE POLYNEUROPATHIES

Throughout this treatise reference has been made under the individual disease entities to the polyneuropathy associated with that particular disorder, whether it occurs commonly or infrequently This term is to be preferred to the designation of 'polyneuritis' since the true inflammatory neuritides are less common than the pathologic condition of the peripheral and autonomic nerves which results from toxic metabolic and ischemic processes [1135 1138] The diagnoses of poliomyelitis, trichinosis dermatomyositis and myasthenia gravis are frequently entertained in the early clinical phases of a polyneuropathy Attention is again directed to the entity

known as "carcinomatous neuropathy" which may present itself as a subacute cerebellar degeneration, a sensory neuropathy, or various neuromuscular disorders (motor neuropathy and myopathy)—in addition to the picture of a polyneuritis [16 3] It has been observed not only in the presence of carcinomatous disease, but also with proven lymphoma, leukemia, and myeloma [672]

The diverse causes of *polyneuropathy* are reviewed in the following listing

1 *Metabolic disorders*
   Beri beri (p 42)
   Pellagra (p 43)
   Chronic alcoholism
   Diabetes mellitus (p 71)
   Porphyria (p 61)
   Amyloid disease (with or without an underlying myeloma or lymphoma) (p 59)
2 *Hematologic disorders*
   Combined system disease (p 191)
   Sickle cell disease (p 195)
3 *Infections*
   Diphtheria (p 161)
   Infectious mononucleosis (p 198)
   Leprosy (p 176)
   Infectious polyneuritis
   The leptospiroses (p 157)
   Herpes zoster (p 523)
   Trichinosis (p 173)
4 *Neoplasms*
   Metastases (especially bronchogenic carcinoma)
   Multiple neuromas (von Recklinghausen s disease)
5 *Vascular and collagen diseases*
   Polyarteritis (p 307)
   Lupus erythematosus (p 305)
   Thromboangiitis obliterans (p 216)
   Arteriosclerosis
   Thrombohemolytic thrombocytopenic purpura (p 218)
6 *Familial polyneuropathy*
   Peroneal muscular atrophy
   Progressive hypertrophic polyneuropathy
   Refsum s syndrome (*vide infra*)
7 *Granulomata*
   Sarcoidosis (p 204)
   Wegener s granulomatosis (p 207)
8 *Poisons*
   Arsenic (p 68)
   Lead (p 65)
   Mercury (p 68)
   Bismuth
   Methyl alcohol (p 67)
   Triorthocresylphosphate (T C P)
9 *Allergies*
   Serum sickness (p 63)
   Prophylactic immunization (tetanus typhoid paratyphoid pertussis diphtheria rabies)[1137]
10 *Generalized hypothermia* (p 446)[1137b]

The importance of an accurate family history is once again pointed out in the instance of the patient with a complex chronic polyneuritis

Specific reference is made in this regard to the unusual hereditary neuropathy known as *Refsum's syndrome*. The several families that have been stigmatized by this disorder have shown retinitis pigmentosa, progressive nerve deafness, ichthyosis, a high cerebrospinal fluid protein, and epiphyseal dysplasia in various joints, as well as the progressive weakness, wasting and sensory changes in the limbs.[1138]

DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM

A number of the diseases listed above may also evidence involvement of the autonomic nervous system, particularly diabetes mellitus and amyloidosis. These nerve structures have on occasion also been significantly affected by other disorders such as retroperitoneal abnormalities (tumors, inflammation, hematoma) and incontinentia pigmenti (p. 425).[1157, 1158] Marked ileus (Ogilvie's syndrome) has characterized the former process (p. 502).[1370]

"Primary Autonomic Insufficiency"

The syndrome of "primary autonomic insufficiency" is characterized by orthostatic hypotension, hypohidrosis and impotence. It closely simulates the effects of a therapeutic block of ganglionic transmission.[1139] This disease is distinct from the postural hypotension associated with general debility, diabetes mellitus, Addison's disease and various neurologic disorders. The lesion in primary autonomic insufficiency is diffuse, involving both sympathetic and parasympathetic components. It is of great interest that vasopressin can significantly raise the blood pressure of these individuals—in contrast to the absence of a pressor response with this agent in normal subjects.[1139b]

Dysautonomia

The syndrome of dysautonomia has been recognized less than a decade. It can present as a baffling diagnostic problem to pediatricians and internists who are not familiar with this entity. Dysautonomia may appear in the fully developed clinical state or as milder variants and "formes frustes." Jewish patients have comprised the majority of the cases reported to date. It is not unlikely that this condition will ultimately be found to represent a mendelian recessive characteristic.

Various evidences of autonomic dysfunction are found. These include excessive sweating, emotional instability, evanescent skin blotching, poor temperature control, vomiting crises and episodic hypertension with postural hypotension.[1140] The most frequent identifying feature of this disease consists in the absence of lacrimation ("crying without tears"). Other bizarre manifestations are probably a result of diffuse brain involvement—namely, hyporeflexia, generalized motor incoordination, marked difficulty in swallowing, urinary frequency, a relative indifference to pain, corneal ulceration, syncopal attacks, extreme muscular weakness and abnormal electroencephalograms.

Some idea as to the difficulties encountered in diagnosis may be had by the following brief listing of the initial diagnoses that have been made in these cases amyotonia congenita, cystic fibrosis, pyloric stenosis, tracheoesophageal fistula, pheochromocytoma, renal anomaly, cerebral birth injury, and schizophrenia [1140a]

TUMORS OF THE VAGUS NERVE

While tumors of the vagus nerve are infrequently encountered even by neurologists and neurosurgeons, a brief résumé of the many deceptive diagnostic variations that might result from such lesions is germane to this text When one considers the long course of the vagus nerves through the neck and thorax and the profound physiologic importance of these structures one can begin to comprehend the extremely varied features which may present themselves These include a localized swelling in the neck or pharynx, hoarseness due to involvement of the recurrent laryngeal nerves, a sensation of pressure in the neck, choking, coughing, pain, a Horner's syndrome, paralysis of the vocal cords, dysphonia, dyspnea, and tachycardia [1141] The tumor might be first discovered as an asymptomatic mediastinal mass The finding of other manifestations of von Recklinghausen s disease under such a circumstance could indicate the neurofibromatous nature of the neoplasm (but does not necessarily affirm the benignity of the process)

Several of these tumors have involved the inferior vagal ganglion (ganglion nodosum) or the associated vagal body ("glomus intravagale") Since this structure connects with branches of the hypoglossal nerve, the superior sympathetic cervical ganglion, and the first and second cervical nerves, many physiologic derangements might ensue For example, chemodectomas of this area have manifested themselves as pain during sneezing, associated with momentary loss of consciousness [1141] Excision is usually in order since these tumors are generally resistant to roentgen therapy

THE NEURODERMATOSES

Brief mention will be made of that interesting group of diseases known as the neurodermatoses (phacomatosis), which includes neurofibromatosis (von Recklinghausen s disease), the von Hippel-Lindau disease, the Sturge-Weber syndrome, and tuberous sclerosis Although the multiple germinal dysplasias are also listed under Group XIV (p 419), this group of ectodermal developmental defects is cited here inasmuch as, by definition, both the nervous system and the skin are involved The variation is great with possible involvement of the cutaneous subcutaneous skeletal, vascular, and lymphatic systems Other congenital anomalies are also commonly noted

In addition to the hemangiomatous malformations of the central nervous system and the retina in the *von Hippel Lindau disease*, skin telangiectases and pancreatic or mesenteric cysts may be present [1142]

Cutaneous nevi overlying the superior and middle branches of the trigeminal nerve are characteristic of the *Sturge Weber Dimitri syndrome*

(encephalotrigeminal angiomatosis) Other features include hemiplegia, convulsive seizures, mental deficiency, unilateral glaucoma or exophthalmos, and a unique type of intracranial calcification that follows the convolutions of the cerebral cortex on the affected side

The cutaneous manifestations of the Sturge-Weber-Dimitri syndrome are depicted in Figure 65 (Atlas page 41)

Neurofibromatosis has proved to be not at all a rare finding in the author's own practice Its familial diathesis and the frequent association with pheochromocytoma were mentioned under Group I (p 22) [1145] This type of von Recklinghausen's disease is occasionally associated with alopecia, feeblemindedness epilepsy, pigmentation and scoliosis [1143, 1144] The term "phacoma" refers to the flat oval tumor that may be found on the retina in this disease

The so-called café au lait spots may precede the multiple fibrous tumors by several years, or they might even occur without the latter in the incomplete forms of neurofibromatosis Crowe and Schull have stated that this disorder can be presumed to be present if more than six such spots are found each one exceeding 1 5 cm in its broadest diameter [1146] The lower end of the femur is a frequent site for the bone lesions

The cutaneous manifestations of neurofibromatosis are depicted in Figure 28 (Atlas page 18)

Tuberous sclerosis is characterized by epilepsy multiple intracranial calcifications, mental retardation, adenoma sebaceum and a variety of dermatologic lesions The term "tuberous" refers to the gross "potato-like' appearance of the involved cerebral cortex Further reference to this disorder is made under Groups XIV and XVII (pp 426 and 543)

Adenoma sebaceum in tuberous sclerosis is depicted in Figure 67 (Atlas page 42)

GROUP XIII

Iatrogenic Illness

GENERAL CONSIDERATIONS

Misinterpreted Laboratory and Radiographic Findings

Misdiagnosis and Incorrect Prognosis as the Basis of Iatrogenic Illness

Abuse of the Concept of Noli Me Tangere

The Reasonable Calculated Therapeutic Risk

The Adverse and Paradoxic Effects of Drugs

THERAPEUTIC PROCEDURES PRODUCING UNDESIRED LONG-TERM SEQUELAE

Multiple Immunizations

Potentially Sensitizing Immunizing Biological Products

Chemicals Added to Food

Fluoridation

Radiation Sequelae

General considerations pertaining to the long term systemic effects of ionizing radiation Dosages of patient exposure during diagnostic procedures Hematologic effects Cataracts Dental defects Congenital anomalies Genetic mutations Carcinogenesis Therapeutic radiation Irradiation for benign lesions X-ray to spine Hazards to physicians and other radiologic personnel Radiation pneumonitis Radiation nephritis Radiation enterocolitis Radiation proctitis Radiation esophagitis Squamous cell carcinomas of mucous membranes Radiation pericarditis Radiation myelitis Radiation osseous reactions Chronic radium poisoning Erythema multiforme, herpes zoster, and dermatitis herpetiformis

SEQUELAE OF DRUG THERAPY

Allergy

Most drugs in varying degrees of frequency Manifold variations affecting the skin, bone marrow, lungs liver, kidneys small blood vessels and joints (Also see Groups II and VIII)

Intoxications

Sulfhemoglobinemia and methemoglobinemia (p 516) Aniline derivatives Benzene derivatives Sulfonamides Nitrites Nitrates

Secondary hemochromatosis (p 61)

Prolonged iron therapy Multiple transfusions

Mercurial poisoning (p 68)

Prolonged use of the oral mercurial diuretics (p 251)

Hypervitaminosis A Vitamin D poisoning Bromide poisoning (p 64) Atropine poisoning Neostigmine poisoning (pp 371 and 481) Digitalis poisoning (pp 244 and 824) Quinidine poisoning (p 274) Salicylate poisoning (p 65) Chronic iodide poisoning

Metabolic and Endocrine Derangements

Injudicious use of cortisone, corticotropin and related substances Injudicious use of thyroid substances

Hypothyroidism and thyroid hyperplasia

Phenylbutazone Cobalt PAS Thiocyanates

Injudicious use of testosterone and estrogens

Gynecomastia

Estrogens Digitalis

Hypercalcemia

Prolonged alkali ingestion Vitamin D excess Excessive estrogenic and androgenic therapy

Electrolytic depletions (pp 79 and 246)

Electrolytic excesses (pp 81 and 478)

Deficiency syndromes induced by metabolic antagonists or biologic competitors (p 42)

Folic acid (p 191) Vitamin B_1 (p 191) Isoniazid (p 152) Methionine or niacin in severe liver disease (p 96)

Undesirable Side Effects or Excessive Therapeutic Response

Hemorrhage and purpura

The anticoagulants (p 274) Quinidine Salicylates Ergot Gold Phenylbutazone Acetazoleamide

Eighth nerve damage

Streptomycin Dihydrostreptomycin Neomycin Polymyxin

Jaundice (p 94)

Methyl testosterone Chlorpromazine Thiouracil Tapazole PAS Sulfadiazine Marsilid

Pyloroduodenal obstruction (p 500)

The anticholinergic drugs

Respiratory failure in emphysema asthma and severe kyphoscoliosis (pp 278 and 450)

The narcotics and sedatives

Hypochloremic hypokalemic alkalosis and salt depletion (See Groups II IX and XV) (pp 79 246 and 477)

Vigorous mercurial diuresis and salt restriction in cardiac renal and hepatic disease

Hypoplasia of the bone marrow and agranulocytosis

The anticonvulsive drugs The antihistaminics Chemotherapy The antithyroid drugs Sedatives Gold

Phenylbutazone Nitrogen mustard Chloramphenicol Amphetamine Hydralazine Promazine

Cerebral thrombosis (p 360), hypotension, myocardial infarction (p 431), and severe interstitial pulmonary fibrosis (p 130) due to intensive antihypertensive therapy

Severe mental depression and parkinsonism

The rauwolfia and chlorpromazine (Thorazine) preparations

Urinary retention

The ganglion blocking agents The anticholinergic drugs The antihistaminics Isonicotinic acid hydrazide

Urinary calculi

Leukemia therapy with TEM and the antifolic acid compounds Milk alkali therapy (p 406) Excessive calcium or vitamin D

Acute tubular necrosis ("lower nephron nephrosis") (pp 54 and 458)

Quinine Sulfonamides Rhus injections Edathamil calcium-disodium Parenteral bacitracin neomycin, and polymyxin

Collagen disorders and "hypersensitivity angiitis" (pp 295 and 304)

Sulfonamides Gold Hydrazinophthalazine Thiouracil Various sera The hydantoins Cortisone

Peripheral neuritis

Arsenical compounds (p 68) Stilbamidine Various sera

Toxic hepatitis

Phenurone Phenylbutazone Isonicotinic acid hydrazide

The nephrotic syndrome (p 55)

Tridione Paramethadione Edathamil calcium disodium Hypertonic solutions of sucrose, glucose, urea, and acacia

Photosensitization (p 523)

Sulfonamides Barbiturates Gold Quinine Coal tar dyes

Gastrointestinal hemorrhage

Salicylates (p 497) The adrenocortical steroids and corticotropin (p 499) Reserpine (p 498) Phenylbutazone (p 498)

Complications of Antibiotic Therapy (p 138)

Resistance Alterations of flora Superinfection Interference with antibody formation Pseudomembranous enterocolitis and tracheobronchitis

Complications of Blood Transfusions (p 461)

Infectious hepatitis Hemochromatosis Gram negative in

fections Hemolytic reactions Malaria Citrate intoxication

Addiction and Habituation (pp 392 and 474)

Opiates Barbiturates Tranquilizers

The Systemic Complications of Topical Dermatologic Therapy

Boric acid intoxication Salicylic acid poisoning Phenol poisoning Mercurial poisoning Estrogenic effects "Broadening of the allergic base" Exacerbation of anhidrosis with heat hyperpyrexia

GENERAL CONSIDERATIONS

THERE is probably no better indication of the current importance of this group of diseases than the manner in which the term 'iatrogenic" has been transported from the medical dictionary to the tongue of the practitioner within the past few years The above listing—which is obviously far from complete—should suffice in itself to impress one with the magnitude of the problem, particularly for the medical consultant The new syndromes which continue to emerge with increasing prominence as a result of the development of potent new therapeutic agents improved surgical techniques and more efficient equipment are properly captioned "diseases of medical progress "[1147]

A number of the potential iatrogenic hazards in the treatment of several common medical disorders are elaborated upon elsewhere in the text In this regard, particular attention was directed to the management of heart failure (p 243) the management of myocardial infarction (p 273) and the management of diabetic acidosis (p 71)

Before discussing several of the specific iatrogenic disorders that were enumerated above, a few comments upon the entire general subject are in order While *it is almost an inevitable shortcoming of discussions of this* type, the ivory tower type of dissertation will be avoided here As a privately practicing internist I am fully cognizant of the inevitable fallibilities of the physician in diagnosing and treating puzzling illness These deficiencies apply not only to conscientious and well trained clinicians engaged in solo practice but also to members of large clinics and university groups where the impact of the element of human error tends to be buffered somewhat It is my conviction that emphasis on and awareness of this problem by all physicians will significantly contribute to both the understanding and prevention of much iatrogenic illness

Bogdonoff has aptly stressed the subtle and profound effects which the physician s psyche may exert upon the patient s "soma ' particularly in ' difficult' cases This obviously undesirable relationship often stems from subconscious feelings of hostility or challenge He has also demonstrated how such attitudes might actually alter his clinical judgment in management under these circumstances[1077b]

MISINTERPRETED LABORATORY AND RADIOGRAPHIC FINDINGS

The theme of "*laboratory procedures as an emotional stress*" is further amplified in the introductory remarks to Part II of this book Considerable emotional distress has been wrought and a tremendous quantity of therapy is continually and needlessly prescribed by the misinterpretation of "low" hemoglobin values, "low" metabolism rates, and "low" blood pressures most notably in anxious women In regard to the first, it is quite likely that the currently accepted levels for normal women are too high and will have to be revised downward (to 4 37 million for the red blood cell count, and to 12 5 gm for the hemoglobin)

The same unnecessary apprehension is often provoked by the finding of a prolapse of the gastric mucosa into the duodenum, diverticulosis of the second and third portions of the duodenum diverticulosis coli, and a number of other overinterpreted radiographic findings which are usually asymptomatic and incidental The following listing of additional benign processes, whose x ray appearances have suggested serious and unwarranted diagnoses to the uninitiated, has been extended for purposes of emphasis In these instances—as should be the case whenever *any* laboratory studies conflict with considered clinical judgment—repeat studies, with or without special techniques, can be of decisive value

1 An isolated ringlike structure in the cecum due to an *inverted appendiceal stump* may be labeled cecal carcinoma [1148]

2 *Giant gastric rugae*[1149] and *bezoars*[1150] may resemble malignancy of the stomach but can usually be differentiated by simple fluoroscopic maneuvers The clinician should be alerted to the latter diagnosis in the patient who has had all his teeth extracted recently and who has been swallowing food (particularly orange pulp) without chewing it—a condition aptly referred to as the '*no-teeth*' *syndrome* [1150b]

3 The presence of *hypertrophied Brunner's glands* [1151] *aberrant pancreatic tissue*,[115] and *hyperplasia of the lymphoid follicles in the first portion of the duodenum*[1153] may produce a scalloped or pseudopolypoid appearance that is apt to be diagnosed as peptic ulcer or neoplasia

4 An *esophageal phrenic ampulla* is not infrequently labeled hiatal hernia

5 *Tomato seeds in the colon* have been diagnosed as ulcerative colitis

6 There has recently developed a tendency to overinterpret the significance of a *prolapse of the gastric mucosa* into the duodenum, particularly in regard to bleeding and other gastrointestinal symptoms This actually represents a physiologic phenomenon that is of *no* clinical import *per se* in the great majority of instances in which it is noted [1545]

7 The striking shadows occasionally produced in *chest films* by an azygos vein, other anomalous septa of the lung, the nipples, the manubrium, the scalloping and hepatic herniation of the diaphragm and skin lesions or locks of hair on the chest wall are findings that frequently alarm physicians interpreting these x rays Clinicians should insist upon frequent and repeated chest films for the patient suspected of having *minimal* pulmonary tuberculosis on the basis of one or two chest films in order to avoid an unnecessary iatrogenic emotional upheaval The author has frequently

observed instances of this nature where the shadows in question proved to be transient atelectases (especially in asthmatic patients) or technical artifacts

8 The *unilateral congenital absence of the pectoral muscle* creates an increased radiolucency of one lung field that has been misinterpreted as pulmonary emphysema pneumothorax, cystic disease of the lung and absence, hypoplasia or thrombosis of a pulmonary artery [1154a]

9 In a surprisingly significant number of patients that my radiologist colleagues and I have seen in consultation, the failure to appreciate the presence of a *pes excavatum* in a single posteroanterior chest film had resulted in the diagnosis of congenital heart disease or a pulmonary mediastinal pathologic condition being made [877]

10 All the "pathognomonic" signs of bone malignancy can be mimicked by a number of *developmental osseous defects* [1155] This is particularly true of the "double-contour effect," which represents a local exaggeration of the normal appositional growth of bone—most notably in underweight or premature infants Similarly the discovery of either "roughening" and "abrasion" of the posterior aspect of the lower end of the tibia, or cortical defects (single or multiple) in teen agers has frequently engendered much apprehension because of the suggested diagnosis of a malignant bone tumor

11 Keats has set forth the following four anatomic variations which he considers to be of importance to radiologists [1154b]

Large diploic venous lakes of the occipital bone (which may simulate cystic lesions and various tumors)

Variations in the x ray appearance of the caudal end of the sternum (which may simulate a destructive lesion of this bone)

Simulation of a fracture of the calcaneal tuberosity by the apophysis in the oblique projection of the foot

Visualization of the pericardial shadow on the right cardiac border

Misdiagnosis and Incorrect Prognosis as the Basis of Iatrogenic Illness

A few additional allusions to the subject of misdiagnosis as the basis of iatrogenic illness will again point out its importance

1 Most clinicians harbor considerable diagnostic respect for infection with *Entamoeba histolytica* (p 171) Nevertheless, the impact of surveys revealing the high incidence of amebiasis from areas which do not represent more than a small segment of living conditions in the United States (military environs, penal institutions, asylums, slum areas) has left in its wake the problem of *amebaphobia* to further complicate the lives of many patients suffering solely from functional gastrointestinal disorders [1156]

2 The diagnosis of '*multiple food allergy*' is often based upon positive skin reactions of questionable significance to the extracts of many foods Too great emphasis on this type of skin testing all too commonly has resulted in the patient being unnecessarily maintained on extremely restricted diets often to the point of malnutrition

3 Perhaps the commonest and the most serious iatrogenic disease prevalent today is "*heart disease of electrocardiographic origin*" [1157] In an era so stigmatized by the prevalence of degenerative cardiovascular dis-

orders as is the present one, it is virtually an impossibility for both the patient *and* the referring physician to be completely reassured by the consultant when primary chest wall tenderness is found to be associated with minor but stable S T segment or T wave changes

The emotional adjustment of many patients suffering from chronic disease is often needlessly hindered These individuals are subjected to anxiety and loss of hope because of the little thought given by some physicians to the mental impact of an *inconsidered prognosis* For example, it has been amply shown that the life span in chronic lymphatic leukemia remains essentially the same on a statistical basis whether no "specific" therapy, x-ray therapy, or chemotherapy is used [1158] To subject such an individual—particularly the asymptomatic case in the older age groups that is accidentally discovered—to blood counts every few weeks and to numerous expensive and nonspecific therapies without positive and optimistic reassurances may be a gross injustice

In his treatise on the natural history of disease, Ryle has set forth the following apt remarks on prognosis "Prognostic ability is born largely of pathology and patiently gathered clinical experience It evolves even more slowly than diagnostic ability Minute and careful clinical observation, a good visual memory, and that necessary inquisitiveness about the subsequent course of cases may all be numbered among the handmaidens of prognosis "[1169] Even though no doctor lives long enough to write a good book on prognosis (to paraphrase Sir James Mackenzie's remark), it is well to remember that the art of prognosis is often as important as the diagnosis itself

Abuse of the Concept of Noli Me Tangere

The concept of *noli me tangere* should never be knowingly abused Several instances of the harm induced by unnecessary or overaggressive therapy will now be cited

1 A number of strokes have followed the arbitrary use of the more potent antihypertensive preparations in the presence of a long standing, labile, and adequately compensated hypertension, especially in elderly patients *Iatrogenic hypotension* of this type is particularly dangerous in individuals with insufficiency of the basilar artery vertebral artery network due to the resulting inadequate perfusion within the existing collaterals (p 360) [1089]

2 Many writers have correctly deplored the use of *"cosmetic" transfusions* as a convalescent tonic by physicians who fail to appreciate the numerous and potentially serious complications stemming from this mode of therapy Of the latter, homologous serum hepatitis heads the list There has been a tendency to overtransfuse patients with chronic diseases (chronic leukemia, azotemia, and the like) in an attempt to bring the level of the hemoglobin up to 15 gm per cent In reality most of these individuals can often be readily stabilized without symptoms at levels of 10 or 11 gm per cent

3 The reduction in therapeutic effectiveness, the added cost, and the potential dangers of *multiple ingredient preparations* are occasionally im

portant considerations[1304, 1160] This issue is exemplified by the increasing frequency of combined system disease subsequent to the use of multivitamin combinations containing folic acid (p 191)[695] Similarly, there is a potentially enhanced ulcerogenic effect of salicylates by their incorporation into a number of preparations with the adrenocortical steroids (p 499)

4 Careful studies in a number of laboratories of the purported superior antibacterial activity of *antibiotic mixtures* that contain a tetracycline compound with either erythromycin oleandomycin, or spiromycin have failed to support such claims[1162] Furthermore the patient may suffer from such therapy because these paired antibiotics may in fact, impart a markedly inferior degree of antibacterial action

5 The rate of progression of a chronic lymphocytic leukemia may be enhanced by a *splenectomy* This procedure can also produce very dire consequences in patients with myeloid metaplasia of the spleen when the indications are not well founded (p 203)[738]

6 Physicians must continually be aware of the numerous implications attendant upon the unnecessary insistence on excessive rest, particularly in the older age groups Phlebothrombosis osteoporosis, renal lithiasis, atrophy of the heart, and muscular wasting are but a few of the complications due to *hypokinetic disease*

7 One should always bear in mind the *possible teratogenic effects* (particularly cleft palate) upon the fetus by the unnecessary exposure of women in their first trimester of pregnancy to x rays, vitamin deficiency, cortisone administration, radioiodine, and hypoxia[116]

8 Similarly the relationship between the prolonged administration of oxygen therapy to newborn infants and the development of *retrolental fibroplasia* is now well documented by numerous observers[116 d]

9 Considerable emphasis is elsewhere placed upon the universally high incidence of *iatrogenic pyelonephritis* that results from the routine and indiscriminate catheterization of patients especially in the preoperative or post operative states and in the prepartum or postpartum states (pp 111 and 458)[383, 391, 397] This is a particularly dangerous practice when dealing with elderly patients who may already be subject to some residual volume, and is obviously further compounded by the placement of an indwelling catheter Direct aspiration of the urine from the urinary bladder after the abdomen has been opened and the use of as few individual catheterizations postoperatively as is possible could obviate this complication to some extent

10 Widespread *vascular and "panmesenchymal lesions* can occur in certain susceptible patients with rheumatoid arthritis—and possibly also in disseminated lupus erythematosus—either while they are being maintained on large doses of cortisone, or as this drug is being withdrawn from them (p 14)[17]

The Reasonable Calculated Therapeutic Risk

On the other hand physicians are occasionally justified in subjecting patients to the reasonable calculated risks of certain potent therapies In

these instances, close observation can usually obviate a full blown exfoliative dermatitis, angitis, renal damage, or the effects of bone marrow suppression and destruction For example, situations of such magnitude might arise from the progressive infection caused by certain resistant organisms that the parenteral use of the nephrotoxic "antibiotics of desperation" (bacitracin, neomycin, and polymyxin) is in order Similarly, adrenal steroid therapy is occasionally justified in certain desperate situations, notwithstanding the presence of a relative contraindication (i e, peptic ulcer, heart failure, osteoporosis, severe hypertension, diabetes mellitus, uremia, hypercholesterolemia, and even active tuberculosis) The supportive role played by these hormones when they are given over short periods in the management of moribund patients with cerebral infarctions, severe liver disease, subacute hemiplegias or pseudobulbar palsies, fulminating polyneuritis, and serious infections has proved to be dramatic and effective

It has been aptly stated that under conditions such as those just enumerated in which potent therapies are being considered that "soul searching is often fully as important as researching"

The Adverse and Paradoxic Effects of Drugs

Only very recently have physicians become cognizant of the important fact that *placebos* can at times produce striking subjective and objective toxic effects, as well as demonstrating remarkable therapeutic power[1163] The author has witnessed *the 'alert reaction'* following the use of many therapeutic agents and has come to expect its occasional occurrence from practically any effective drug For example, one report cites three cases of a paradoxic reaction to meprobamate, in which extreme excitement rather *than tranquilization was produced*[1164a]

The therapist is reminded of the salutary effect rendered by occasional "*therapeutic holidays*" when patients are being given potent medications on a long term basis This is an especially valuable technique when dealing with elderly individuals, since it simultaneously allows for a period of rest while enabling the physician to re-evaluate the status of the basic problem from time to time These intervals also enable one to recognize a *physical dependence upon drugs* relatively early Nowhere is this better exemplified than with prolonged barbiturate, thyroid or estrogen therapy[1160] Several recent reports have pointed out the true physical dependence that can be created by large doses of meprobamate (and probably the other tranquilizers), similar to the situation with barbiturate addiction[1164b, d] This consideration must be particularly borne in mind when these agents are prescribed in large amounts on a refillable basis for either alcoholics or previously known drug addicts Fortunately, there is no indication to date that either chlorpromazine or reserpine is addicting[1164b]

Instead of such striking manifestations as grand mal type convulsions and a delirium resembling that of alcoholic delirium tremens following the abrupt withdrawal from barbiturates (which might even prove to be fatal) there may be "minor" symptoms These include anxiety, involuntary twitching of muscles, coarse intention tremors nausea vomiting weakness dizziness, insomnia, and precipitous drops in the blood pressure re-

lated to changes in position. One of the interesting features of physical dependence to the barbiturates consists in its relationship to the amount consumed—i.e., 0.4 gm. daily of secobarbital or pentobarbital, 0.8 gm. or more of amobarbital, and 1.2 gm. or more of barbital are the minimal addictive doses usually required.[1164]

The author harbors the opinion that the continued *excessive reliance upon pharmacotherapy for the management of obesity*—to the exclusion of a sincere effort to comprehend the patient's psychological framework and repeated detailed discussions concerning the use and many abuses of dietotherapy—is practically always doomed to failure, whether the anorexigenic agents or other drugs are employed. Two important and serious sequelae of such management relate to the undermining of the patient's confidence in dietetic management, and the hazards of iatrogenic hypothyroidism that stem from the prolonged and indiscriminate use of thyroid substances (*vide infra*).

On rare occasions *allergies* (such as a generalized erythematous dermatitis of the bullous type) have paradoxically resulted even from the administration of the antiphlogistic hormones, cortisone and prednisone.[18, 1166] The broad ramifications of drug allergy are considered under Group II (p. 62).

It is not at all unusual for the patient who has been seriously ill or who has undergone major surgery to have received from 20 to 40 different drugs. Among these, the anesthetics, the sedatives, the narcotics, numerous antibiotic and chemotherapeutic agents, hormones, pressor agents, cardiac drugs, anticoagulants, antihistaminics, and transfusions or infusions come to immediate recall. Similarly, it is common for a patient undergoing a comprehensive modern diagnostic workup to be subjected to two dozen or more separate tests.

In a recent address entitled "Hazards of Modern Diagnosis and Therapy—The Price We Pay," Dr. David Barr has reviewed this ever increasing problem.[116] He found that of 1000 patients admitted to the medical service of a large hospital, more than 50 major toxic reactions and accidents consequent to diagnostic or therapeutic measures were encountered. "These accidents, risks, and dangers may be regarded as the price that we as responsible physicians must pay for the inestimable benefits of modern diagnosis and therapy."

Along these lines, however, it should be stressed that extreme degrees of "therapeutic paralysis" can be just as detrimental to patients as over-aggressive pharmacotherapy. The happy medium can only be achieved by study, experience, conscientiousness, and eternal vigilance. Such an orientation justifies the anticipation and active treatment of possible therapeutic complications in those instances where "relative" contraindications to certain therapies exist if cooperative patients (who are made aware of these possible risks) are not to be deprived of life-saving or deformity-preventing drugs. This applies, for example, in the individual with active rheumatoid arthritis who requires corticoids in spite of a previous or active duodenal ulcer, and in the patient with Addison's disease who requires cortisone notwithstanding the tuberculous nature of his adrenal disease.

THERAPEUTIC PROCEDURES PRODUCING UNDESIRED LONG-TERM SEQUELAE

One of the most unfortunate aspects of modern drug therapy is the prolonged period of time necessary to scientifically and statistically prove the relationship of therapeutic or toxic drugs and chemicals to their long term sequelae This is particularly a problem when time-tested procedures or agents are incriminated It is very difficult for the conscientious physician to overlook repeated case reports of significant complications following a particular therapy, notwithstanding positive statements of reassurance from the manufacturer that such associations are purely coincidental A case in point within the past few years has been the goitrogenic effect noted following the use of cobalt in the nonspecific treatment of anemia, especially in children[1167]

A related consideration is the well known problem of the time required to modify the dosages and indications of newly introduced drugs once their undesirable effects in humans have become apparent Nowhere can this challenging issue to the therapist be better delineated than when attempts are made to alter the body's endocrine "autopharmacology" with "physiologic doses of the newer hormones (p 14)

Several additional examples of this important issue—factual or suspected—will now be cited

Multiple Immunizations

It has been most reasonably conjectured that the peak incidence of lymphatic leukemia found in infants and children might well be related to the enhancement of this disease by previous multiple immunizations and other therapeutic "stresses"

Potentially Sensitizing Immunizing Biological Products

Physicians must resist the temptation of acquiescing both to hysterical propaganda and to lay pressure in the case of the ever increasing number of potentially sensitizing immunizing biological products While there appears to be little reason for withholding poliomyelitis immunization because of the small amounts of penicillin contained in the Salk vaccine the indiscriminate and arbitrary injection of whole segments of the population with such substances as the egg protein containing influenza vaccine is quite another matter

Chemicals Added to Food

Clinicians should be aware of the fact that between 550 and 700 chemicals are being currently added to food during its production, processing, and storage (preservatives antioxidants, stabilizers dyes, flavoring agents, nutrient supplements), and that the long term effects of a great number of these agents are not yet known[1170a] In view of the current high incidence of gastrointestinal cancer and the enormous amounts of these

chemicals used in the production and processing of foodstuffs—many of which are definitely known to be carcinogenic for animals—it is not unlikely that prolonged studies might demonstrate an actual relationship to exist in humans.[1170c] There already exists highly impressive data from studies carried out in animals that the ever growing tendency to preserve meat, fish, and other food with antibiotics may compound the incidence of antibiotic-resistant organisms. Even though negligible amounts of estrogenic activity are found in food as a result of the use of these particular hormones to improve weight gain and feed efficiency in beef cattle and poultry,[1170b] there are potential hazards in such practices stemming from the exposure of personnel and mistakes in mixing and feeding (p. 409).[1190]

Fluoridation

Similarly, an increasing number of physicians and public health authorities are beginning to ponder the long term effects of water fluoridation. It has been known that an excess of this anticariogenic element can induce changes in the gastrointestinal tract, the central and peripheral nervous systems, and the locomotor tissues. *Fluoride osteosclerosis* is now being frequently encountered by radiologists in patients coming from areas where there is an excessive fluoride content in the drinking water (i.e., greater than 4 ppm.). At the present time, however, there appears to be no harmful effect from such changes or any correlation between the clinical picture and the findings on x ray. Calcification of the sacrospinous and the tuberospinous ligaments has proved to be a distinct aid in the diagnosis of this entity in the patient who is found to evidence asymptomatic sclerosis of the bone.[1171]

Radiation Sequelae

It is an unfortunate but foregone conclusion that an ever increasing proportion of obscure disease in the near future will prove to be the result of excessive exposure to radioactive substances during the course of industrial, military (including radar), diagnostic, and therapeutic contact. This consideration was emphasized even prior to the atomic era by the number of significant complications following x radiation therapy, many of which are still not fully appreciated. Consequently, it is most pertinent in this volume to dwell upon such undesired effects as they affect nine different organs—namely, radiation pneumonitis, nephritis, enterocolitis, esophagitis, pericarditis, myelitis, and the mucous membrane and osseous bone marrow changes induced by radiation. Chronic radiodermatitis will be considered under "Cutaneous Medicine" (p. 558). Since the clinical onset usually follows a latent period that varies between two to eighteen months from the actual radiotherapy, these manifestations are apt to be attributed to metastases or to other complications of the original disease.

Several preliminary comments of general interest to all physicians are in order concerning both the *dosage* and the long range effects of ionizing radiation, many of which we have only just begun to appreciate. All radioactive substances, whether in the form of natural radium or the arti

ficially produced isotopes, emit rays Of these, the gamma rays are the most important from the pathogenic and genetic standpoints

It is estimated that the average exposure of the gonads during the first thirty years (during which time parents have the majority of their children) is about 5 r from natural "background radiation" and about 3 r from diagnostic x-rays The problem can be quickly appreciated when these figures are considered in light of the fact that the gonads may receive as much as 4 r in males and 1 2 r in females during the course of a single barium enema Even with the customary shielding during x ray therapy as the latter is generally administered for extragenital dermatologic lesions, the gonads receive significant amounts of stray radiation

In another detailed report of the gonadal doses received during radiographic examinations from ten x ray units at the Massachusetts General Hospital (with a total filtration of at least 2 5 mm of aluminum), the following average microroentgens received by the gonads per film were recorded [11 3t]

One gains some idea of the radiation absorbed (as measured in air at the point of entry into the body) when the dose of 0 05 r to 0 1 r for a chest

MICROROENTGENS RECEIVED BY GONADS

	Males	Females
Conventional P A chest film	0 01	0 2
A P film of abdomen	12 0	125 0
Gastrointestinal series (I A film)	3 0	50 0
Barium enema (I A film)	30 0	190 0
Lumbar spine (lateral)	40 0	240 0
Hip (lateral)	2100 0	410 0

film is compared with that of the following procedures fluoroscopy, 10 to 20 r per minute, intravenous pyelography, 7 to 8 r for six films, a barium enema or upper GI series 10 to 20 r per minute for fluoroscopy and 1 2 r for each film diagnostic studies for congenital heart disease 140 r or more thymus radiation, 75 to 350 r treatment of acne, 500 to 1000 r per course [1193] Another indication as to the magnitude of radiation received is to be found in the case of the patient with a troublesome duodenal ulcer Such individuals are not infrequently subjected to six or eight fluoroscopic examinations of two or three minutes each, resulting in a total dose that could easily be as much as 400 r [1193e]

Rall has conveniently set forth a listing (p 397) of certain generally accepted doses of radiation for reference purposes

The amount of radiation received by neurotic individuals in the higher economic brackets who subject themselves to repeated series of diagnostic x rays (particularly for functional disturbances of the gastrointestinal tract) and multiple courses of radiation therapy for minor non neoplastic disorders is often alarming For example, it is estimated that 1000 to 1200 r could be delivered during a course of therapy for dermatitis of various causes, 390 r for subdeltoid bursitis, and several thousand roentgens for rheumatoid spondylitis [1193b] Insufficient attention has been

paid to the considerable radiation delivered both to the jaw and to the chest in individuals receiving regular orthodontic care. It is estimated that up to 300 r can be delivered to the jaw during one full mouth series.[1193c] This is particularly a problem when full mouth x-rays are routinely taken twice annually in children.

The seriousness of the *late systemic and genetic effects of ionizing radiation* are of enhanced importance in the case of exposed infants and children. In this situation, one has to be concerned not only with the possibilities of hematologic abnormalities, cataracts, hypoplasia of the dental enamel, delayed dentition, and congenital anomalies,[1161] but also with the induction of genetic mutations and of malignant disease. For example, in an analysis of 1500 children below the age of ten years with malignant disease (especially leukemia), a striking correlation was shown with the incidence of diagnostic abdominal radiation received during the relevant pregnancy.[119] Accordingly, pelvimetry in pregnant women must not be recommended too lightly.

DOSES OF RADIATION

	Roentgens
Body background (per year)	0.020
General background (per year)	0.200
Fallout 1954	0.015
Permissible (per year)	15.6
Chest x-ray	0.100
Lateral lumbar spine	5.7
Fluoroscopy (2 min.)	34.0
Radioiodine tracer	0.005
(10μc-dose in general body radiation)	
Radioiodine therapy for hyperthyroidism	
(average general body dose 10 mc.)	7.0 ± 5
(thyroid dose)	10,000.0

There is a statistically significant incidence of thyroid carcinoma and leukemia associated with previous *irradiation for benign lesions of the head, neck and chest in infants.* This type of therapy is specifically decried when administered for the dubious x-ray diagnosis of "thymus enlargement" (which often disappears after a good inspiratory film is obtained).[1168]

It has been shown in prolonged follow up studies that there is a tenfold increase in the incidence of leukemia in patients with ankylosing spondylitis who have received *x-ray therapy to the spine.*[1169]

Many careful observers are reaching the conclusion that there is no absolutely safe minimal dose of *therapeutic radiation* and that the delayed sequelae of radiation (unlike the acute effects) are not averted by spreading out the total dose (p. 398). One can only wonder if this cause and effect relationship—if proved to be unequivocally true—may not also result from the repeated exposure incurred during such extensive roentgen diagnostic procedures as *cardiac catheterization and angiocardiography.*

The current permissible level of total body radiation accepted by the International Committee on Radiation Protection for x-rays or gamma rays of less than 3 mev energy is 0.3 r per week. This means that for a

thirty year working life at the maximum permissible dose level, there is a total occupational exposure of 468 r[1197] The unfortunate fact remains however—as agreed upon by the leading contemporary geneticists—that although certain levels of exposure are obviously dangerous, there is no such thing as a completely safe level from the viewpoint of potential genetic mutation[1194] Many authorities now believe that every person should keep a lifetime record of his exposure to diagnostic x rays

The alarming incidence of leukemia in radiologists,[663a] in individuals who have received radiation to the neck or chest for a presumed "thymus enlargement" in infancy,[1168] and in patients with rheumatoid spondylitis who have received x ray therapy to the spine[1169] was cited earlier in this chapter The incidence of leukemia in the population surviving the atomic explosions of Hiroshima and Nagasaki is already twelve times greater in those who were near the hypocenters than in the survivors who were at the periphery of the blast areas[663b] Similarly, it has been demonstrated after prolonged periods of observation, that there is a markedly increased rate of pelvic malignancy following irradiation for benign gynecologic diseases or for purposes of castration[1196]

There is yet another aspect of these delayed radiation sequelae that is of unique and profound import to radiologists, urologists, gastroenterologists, and dermatologists who have experienced prolonged occupational exposure This pertains to the definite shortening of life encountered in the e specialists, such as was noted by Warren in a careful analysis of the deaths of 82 441 physicians reported during the period of 1930 to 1954[1197] In the case of radiologists the average age at death was 5 2 years earlier than that of other physicians The observation that radiologists die younger from practically *every* major cause of death—neoplastic or non neoplastic—strongly suggests that ionizing radiation is capable of both lowering one's resistance to disease and of hastening the aging process

Radiation Pneumonitis

In radiation pneumonitis, the reaction is not only dependent upon the total dosage, the rapidity of treatment, and the volume of tissue irradiated but also upon the patient's age and the pathologic processes within the pulmonary parenchyma (especially metastases and intercurrent infection) Treatment over the hilus is more prone to result in extensive fibrosis than when it is directed over the periphery of the lung Injury to the epithelium with the formation of a hyaline membrane, thickening of the alveolar walls, patchy atelectasis vascular changes, and fibrosis have all been observed following the initial inflammatory reaction[1198, 1199] These changes can obviously result in numerous roentgenographic patterns

Impaired diffusion across the alveolar capillary membrane (as manifested by hyperventilation reduced oxygen consumption with exerci e, and elevated dead space measurements with a low arterial $_pCO_2$) probably plays an important role in the functional abnormalities observed[1200] There may be several clues in the chest films to the early reaction These consist of an elevation of the diaphragm (in the absence of fibrosis and atelectasis), with subsequent blurring and indistinctness of its outline The relative stability of the pneumonitis in serial roentgenograms over a subsequent

period of two or more years also tends reasonably to preclude a neoplastic spread

Severe and even fatal radiation pneumonitis and fibrosis has also complicated the administration of large doses of radioiodine for the treatment of pulmonary metastases due to thyroid cancer [1193d]

Radiation Nephritis

A radiation nephritis should be suspected when edema hypertension, renal changes cardiomegaly, and azotemia ensue following intensive x radiation which has included the renal tissue within the therapeutic field [1201] This is especially true when malignant testicular tumors are so treated The widespread fibrosis between atrophic tubules the universal glomerular damage, and the fibrinoid necrotic lesions of the arterioles clearly point out that the prevailing attitude concerning the presumed radioresistance of the kidneys must be tempered somewhat

Radiation Enterocolitis

While radiation enterocolitis is an occasional unpredictable complication of radiotherapy that was directed to the lower vertebrae or to the abdomen *for neoplastic disorders, it primarily follows radiation therapy for* invasive carcinoma of the pelvic organs Its incidence in these cases is estimated at 1 to 2 per cent [1200] The production of mucosal ulceration in a sclerotic and relatively ischemic bowel represents the basic process It may manifest itself as intestinal hemorrhage, focal intestinal necrosis, perforation obstruction diarrhea malnutrition, and superimposed bowel infection In fact, both the clinical findings and the radiographic and gross appearances of this condition can be identical with those of regional enteritis

Radiation Proctitis

A 50 per cent incidence of injury to the bowel is to be anticipated when the tissue dose delivered to the retroperitoneal lymphoid area reaches 5500 r One should be particularly alerted to the possible occurrence of this complication when a concomitant radiodermatitis is provoked Corticotropin has proved of some value in managing this reaction [1202c] The problem of rectal bleeding due to a radiation proctitis secondary to the treatment of carcinoma of the cervix will be considered later (p 498)

Radiation Esophagitis

One may expect to encounter radiation esophagitis more frequently in the future as therapy for intrathoracic cancer with the betatron and with cobalt units becomes more widespread [1203] The histologic changes are most marked in the muscle and the submucosa They are reflected by the narrowed esophageal lumen seen on x ray study The maximum tolerance dose for the esophagus appears to be a total of 6000 r, administered at the rate of no more than 1000 r per week Another unusual complication of radiotherapy administered to the chest is the occurrence of esophageal herpes simplex in patients with cancer of this or other adjacent organs to which large doses of radiation were directed [590]

Squamous Cell Carcinomas of Mucous Membranes

It is not sufficiently appreciated that the epithelium of mucous membranes—like that of the skin—*is susceptible to malignant degeneration* as a late effect of irradiation[1205] This applies to the development of squamous cell carcinomas of mucous membranes both in tissues that were intentionally subjected to external roentgen irradiation, and where such tissues were adjacent to other areas receiving this type of therapy Particular note is made of the frequency with which carcinoma of the gastrointestinal tract is prone to occur in this manner A late radiodermatitis of the skin that was utilized for the external port can be demonstrated in almost every instance

Radiation Pericarditis

Radiation pericarditis should be borne in mind as a possibility in patients who develop a friction rub or an enlarged cardiac shadow after *receiving large amounts of radiation to the chest* This complication is particularly apt to occur when such therapy is directed to the left chest wall following the resection of a breast malignancy Some difficulty might arise in distinguishing it from metastatic disease to the heart

Radiation Myelitis

As noted above and under Group XII, the presence of a radiation myelitis is often not recognized because of the long latent periods involved This diagnosis, rather than that of metastases, should be considered when there are no roentgenographic changes in the vertebrae and when significant spinal fluid changes are not present All segments of the spinal axis may be affected as is indicated by the following central nervous system complications resulting from this mode of therapy[1204] This damage can be averted only *if the radiologist carefully calculates the depth dosage to be* delivered to these structures so that it does not exceed 4500 r

1 *Brain stem damage* following x ray therapy to malignant tumors of the middle ear the pharynx, and the parotid gland Boden found 25 per cent of the patients treated by beam directed techniques—in which multiple small fields were centered on the tumor—were so affected The clinical diagnosis of a cerebrovascular accident was usually entertained

2 *Cervical cord damage* following irradiation for malignant tumors of the nose, mouth, pharynx and cervical lymph nodes Numbness and tingling in the hands and feet precipitated by flexion or extension of the neck and often associated with pain in the neck and shoulders, are almost always present

3 *Thoracic cord damage* may complicate radiotherapy for cancer of the lung or esophagus

4 *Lumbosacral cord myelitis* may ensue following irradiation of the retroperitoneal area for carcinoma of the testis

Radiation Osseous Reactions

Both external radiation and radium intoxication from accidental, occupational, or therapeutic efforts can result in various osseous reactions most notably that of a unique dry necrosis of bone The radiographic

changes are manifest as localized areas of increased density in which multiple areas of rarefaction may also be observed. The jaws, ribs, skull and neck of the femur (at times first manifested as a subcapital fracture) are particularly susceptible. In children who have received fairly large doses of x-ray treatment to fields in which the spine was included, scoliosis might ensue. (Although mature cartilage will withstand radiation relatively well, the growing epiphyseal cartilages in young children are easily damaged. This can result in early epiphyseal closure and permanent skeletal deformity.[1194b])

Osteogenic sarcoma of the skull has followed the irradiation of tumors in or on the skull, particularly where a radiodermatitis was also produced.[1 06] The latent period in a number of these cases often exceeded three years. This points out the importance of avoiding prolonged irradiation for benign lesions, such as postauricular keloids.

Chronic Radium Poisoning

The alpha radiation of chronic radium poisoning resulting from the ingestion of radium paint may ultimately lead to anemia, leukopenia, agranulocytosis, aseptic necrosis and osseous neoplasia (osteogenic sarcoma). From 1930 to 1945 the sol of thorium dioxide was employed in diagnostic hepatosplenography, which—in contrast to radium—is retained in the reticuloendothelial system throughout the remainder of the patient's life.[1 0] There are thousands of people alive today who have had these radioactive materials permanently deposited within their bodies.

Although these particular conditions have fortunately waned as occupational and diagnostic hazards, their clinical counterparts will undoubtedly arise again with the increasing diversion of radioactive materials to industrial and civilian uses. One instance in point which is only now receiving its due emphasis concerns the exposure of technicians to radar. Furthermore, there are a number of hazards associated with the theft, loss, or disruption of encapsulated radium. For example, there have been several reports of accidents involving the escape of radium salts from their sealed containers in the past several years. This resulted in both damage to health and serious and costly contamination of buildings and equipment.[1 07b]

Erythema Multiforme, Herpes Zoster, and Dermatitis Herpetiformis

Erythema multiforme has ensued in from one to twenty-one days following deep x-ray therapy or radium therapy for malignant tumors. This is presumably due to the absorption of the released toxic products that emanate from the induced cellular degeneration.[139] The same association has also been observed with herpes zoster and dermatitis herpetiformis.

Illustrations depicting erythema multiforme, herpes zoster, and dermatitis herpetiformis appear in Figures 8, 18, and 20, respectively (Atlas pages 7, 11, and 12).

SEQUELAE OF DRUG THERAPY

Most of the conditions cited under the introductory listing of iatrogenic illness caused by drug therapy are either self-explanatory or have been previously discussed. It would be in order, however, to elaborate

briefly upon the misuses of six of these drugs, namely vitamin A, vitamin D, the alkalis, atropine, iodides, and the estrogens

Since the induced disorders are at times due to surreptitious self medication on the part of the patient, a careful and detailed history is vital in arriving at the correct diagnosis Experience has repeatedly demonstrated the importance of the manner in which one approaches the patient for a history of possible ingestion of an offending medication Inasmuch as most people consider the term "drug" to be synonymous with one of the narcotics, specific query about the use of various proprietary medications vitamins, "tonics," and home remedies for a host of ailments must be made

Even when self medication is denied by the patient, it may be necessary to examine the blood or urine for either the suspected noxious agent (bromides, vitamin A, barbiturates), or for the possible metabolic derangements resulting therefrom (hypercalcemia, hypoprothrombinemia, hypoglycemia granulocytopenia) The institution of a withdrawal test under close supervision—as described in Section XV of Part II—is occasionally diagnostic Similarly, the therapeutic diagnostic tests listed in Section XIV can aid in clarifying poisoning due to the narcotics, atropine, neostigmine, digitalis, and the anticholinesterases Digitalis intoxication and opiate addiction may also be evidenced by the provocative tests cited in Section XVI

Intoxications

Hypervitaminosis A

Hypervitaminosis A occurs in acute and chronic forms both in children and adults It usually results from the ingestion of large amounts of vitamin A concentrates in the treatment of various skin eye, renal, gynecologic, and ear disorders, and in the optimistic prophylaxis of the common cold [1173, 1174] The clinical manifestations are strikingly reflected in several systems These include the following

1 *Central nervous system*—severe headaches, diplopia, increased intracranial pressure, nausea, vomiting, dizziness, drowsiness nystagmus

2 *Locomotor system*—calcification (with or without true bone formation) of the pericapsular ligamentous tendinous, and subperiosteal structures, decalcification of the skull vertebral bodies, and scapulae In older children, the age group and the lack of mandibular involvement help to distinguish hypervitaminosis A from infantile cortical hyperostosis

3 *Skin*—alopecia seborrhea, exfoliation, hemorrhagic dermatoses, dry and cracked mucous membranes pruritus (may be early and severe), dystrophy of the nails, hyperpigmentation, and coarsening of the skin (due to the follicular hyperkeratosis)

4 *Other changes*—hemorrhagic manifestations (probably due to the induced hypoprothrombinemia), hepatomegaly, splenomegaly, leukopenia, anemia, and increased serum lipids

The cutaneous manifestations of vitamin A intoxication are depicted in Figure 39 (Atlas page 24)

In one review of this subject the case is cited of a twenty eight year old female in whom the following previous incorrect diagnoses were made

over an eight and a half year period brain tumor serous meningitis chronic encephalitis, viral radiculoencephalitis psychoneurosis, generalized infectious arthritis, Addison s disease, dermatomyositis, and hepatitis The symptom complex was found to be due to the ingestion of excessive vitamin A which had been taken for a very mild case of ichthyosis[1173]

Vitamin D Poisoning

Vitamin D poisoning has been observed more than vitamin A poisoning primarily because vitamin D is still used widely in the symptomatic treatment of arthritis and in promoting the healing of fractures[1175] Numerous multivitamin preparations that contain 50,000 units of vitamin D per capsule are readily available for self medication without prescription, and are being promoted by several popular "best-sellers on the subject of arthritis This complication is also a problem in the therapy of some patients with hypoparathyroidism since a number of these individuals will exhibit acute vitamin D intoxication when placed on ordinary doses of this medication The type of vitamin D preparation used appears to bear little relation to the incidence of induced toxicity

The symptom complex of hypervitaminosis D is manifold and is related in large measure to the induced hypercalcemia (p 82) It may include muscular weakness, paresthesias, anorexia nausea and vomiting weight loss, lethargy or depression, headache, pruritus, diarrhea or constipation extensive pigmentation, exfoliative dermatitis, visual and auditory disturbances, a band keratitis, cardiovascular and electrocardiographic abnormalities and hypertension Vitamin D intoxication has been found to be the cause of perplexing normochromic normocytic anemias which had proved refractory to the usual hematinics[18] The anemia in these instances is more an effect of the induced azotemia than either a direct toxic effect on the bone marrow or a hemolytic phenomenon

The urologic changes can be very impressive They include frequency, nocturia nitrogen retention the inability to concentrate, and albuminuria, red cells, and casts in the sediment It is very important to appreciate the potential reversibility in this type of uremia[1176] An astute clinician or radiologist has on occasion suspected this diagnosis upon finding metastatic calcification in such areas as the kidneys, bronchi, stomach blood vessels and the periarticular and subcutaneous tissues The serum alkaline phosphatase is usually normal The blood phosphorus level may be either elevated or decreased

It is stated that the syndrome of idiopathic hypercalcemia of infancy with failure to thrive probably does not represent true vitamin D intoxication, but rather constitutes a hypersensitivity response by certain infants to this vitamin[315] While there is much merit to this point of view, it is also pointed out that many infants undoubtedly receive much more than the recommended 400 to 800 international units of vitamin D daily if one totals up the amounts contained in the fortified milk bread commercial formulas and infant cereals that are ingested—to which large doses of supplementary' vitamins are frequently added in "vitamin hysterical environments

Atropine Poisoning

Atropine poisoning is much more common than is generally realized The universal availability of atropine and the other belladonna alkaloids in a host of applications for ophthalmic, oral, rectal, cutaneous, and subcutaneous use—either in pure form or in mixtures—contributes to this problem Absorption of these agents from the nasal mucosa, applied either directly or via the nasolacrimal duct, is particularly dangerous unless precautions are taken

The manifestations of delirium, fever, disorientation, visual hallucinations, abnormal behavior incoherent speech, dizziness, and lethargy can obviously simulate a wide variety of neurologic, psychiatric, and infectious diseases [1179] The presence of marked thirst, widely dilated and nonreactive pupils, difficulty in urination and the absence of the usual response to methacholine are diagnostic (p 813) The cyclic nocturnal exacerbations of symptoms are at times quite characteristic Physicians must be cognizant of the increased sensitivity to belladonna, atropine, and synthetic drugs of the Artane type which elderly patients with parkinsonism may exhibit, particularly in hot weather [1180]

Chronic Iodide Poisoning

Chronic iodide poisoning or iodism has been encountered less frequently in the postantibiotic era, but still occasionally proves baffling to physicians who are not aware of its clinical scope This condition usually results from the administration of excessively high doses of the inorganic iodide compounds (especially potassium iodide) for supportive therapy in cerebral and respiratory disorders Respiratory manifestations, coryza, increased salivation, soreness of the teeth and gums, skin lesions (iododerma), gastrointestinal complaints, fever, cachexia, and depression characterize the syndrome of iodism Although the iodide ion is excreted independently of chloride—in contrast to the situation with bromide—accumulation will occur in the presence of marked renal insufficiency

Reference was previously made to the concentration of iodides in the saliva and the suggested "reverse thyroid gland" function of the salivary glands in breaking down the thyroid hormone [43] In this regard, it is well to be aware of the entity of "iodide mumps" to avoid needless investigation for mumps or for a stone in the salivary ducts [1184] This represents an occasional idiosyncrasy to the administration of inorganic or organic iodide preparations, particularly following intravenous urography A "radiation parotitis" has even been observed following therapy with radioactive iodine [42]

METABOLIC AND ENDOCRINE DERANGEMENTS

A number of the undesired effects of *steroid therapy* are considered further under Groups I, IV, and XV The more important ones include peptic ulceration (p 199), osteoporosis (p 25), the lowering of the body's resistance to a wide variety of infectious organisms (p 142), edema

adrenal and pituitary suppression (p 14), thrombotic and thromboembolic phenomena (p 77), psychiatric manifestations, panangiitic and pan mesenchymal reactions (p 14), reduced thyroid function (p 14), pancreatic lesions (p 15), and the aggravation of an underlying diabetes mellitus or hypertension Reference is also made to the massive degenerative changes in the weight bearing rheumatoid joints (even with the development of aseptic necrosis or Charcot like deterioration of these structures) which have resulted from their excessive use

At the present time the regular administration of *corticotropin* is being advocated to stimulate the adrenals in patients receiving long term steroid therapy In so doing however, it is not unlikely that endogenous corticotropin production is probably further suppressed with the currently employed excessive dosages of ACTH "boosters" Since the administration of large amounts of the corticosteroids suppresses *both* the adrenocortical function and the production of corticotropin by the pituitary the function of the latter gland can only be re established by subjection of the patient to a period of relative hypoadrenocortisonism following the cessation of steroid therapy [739]

A less appreciated misuse of endocrine therapy is the employment of *I^{131} or thyroidectomy for long standing metastatic thyroid cancer* By presumably inducing myxedema and the subsequent compensatory overproduction of TSH from the pituitary (rather than utilizing thyroid hormone to inhibit this response), the tempo of the spread may be considerably enhanced to the degree of shortening the patient's survival (p 321) [997, 998]

The problem of iatrogenic hypothyroidism (the Farquharson syndrome) resulting from the suppression of endogenous pituitary thyrotropic hormone secretion by the injudicious use of *thyroid thyroxine* and more recently by *triiodothyronine* continues to increase [36] This stems in part from the numerous brochures promoting the favorable results with these agents in the course of short term extensive clinical trials for the treatment of a wide variety of disorders (including obesity and 'metabolic insufficiency') that flood the mail of physicians in a never ending stream

In regard to the undesirable effects of *excessive estrogen therapy*, it is appropriate to preamble any critical comments by reaffirming the obvious great value of these agents in selected cases of atrophic vaginitis, amenorrhea, the menopausal syndrome ovarian agenesis, removal of the ovaries in early life and metastatic disease (particularly when due to cancer of the prostate) Unfortunately all gynecologists and surgeons continue to have the frequent experience of being required to surgically diagnose or treat withdrawal bleeding, carcinoma of the uterus or enlarging breast masses in menopausal and postmenopausal patients who had been given prolonged and large doses of estrogens as an all purpose female tonic" This may be a particularly confusing or hazardous situation in the presence of a familial cancer background hepatic insufficiency and in premenopausal women in whom estrogen therapy is prescribed for either menstrual irregularities or for its alleged prophylactic value against the symptoms of 'the change [1181]

The actual physical dependence created by the long term use of the estrogens—resulting in the precipitation of severe vasomotor phenomena

following their withdrawal—is appreciated by few physicians[1160] The palliative estrogenic treatment of patients with osseous metastases is occasionally followed by serious hypercalcemia This is particularly prone to occur when osteolytic lesions are the object of therapy[310, 311] (p 82) A carefully performed provocative "hormone dependency test" with stilbestrol in metastatic carcinoma of the breast (or with testosterone in the presence of prostatic metastases) may give a preliminary indication as to both the therapeutic and toxic effects of such therapy (p 829)

The development of *gynecomastia* in patients receiving digitalis has been explained in part by the chemical similarity of these cardiac glycosides to the estrogenic compounds[1182] In 17 patients with advanced mammary carcinoma who received considerable estrogen therapy, the induced fluid retention either led to congestive heart failure or exaggerated an existing mild decompensation (p 234)[1183]

Another disorder frequently and unknowingly fostered by physicians is the so-called *milk alkali syndrome* (or milk drinker's disease) which was first clearly defined but a few years ago (1949) by Burnett and his colleagues[1177] The patients so affected almost always give the history of having had a peptic ulcer for many years and of having ingested large quantities of milk and absorbable alkalis during this period The characteristic features of the disease which usually help to distinguish it from primary hyperparathyroidism with secondary kidney damage include hypercalcemia *without* hypercalciuria or hypophosphatemia, a normal serum alkaline phosphatase level, marked renal insufficiency with azotemia, a mild alkalosis, ocular deposits in the cornea and conjunctiva (p 82), metastatic soft-tissue calcifications, pruritus, and an absence of skeletal demineralization The lowering of the serum calcium and the potential reversal of both the renal insufficiency and the metastatic calcification by omission of the milk and alkali are also unique (p 819)[1181] For further discussion of hypercalcemia see page 82

The pathogenesis of this condition—i e , renal impairment secondary to the alkalosis, combined with the increased intake and the decreased excretion of calcium—would seem to be clear cut Nevertheless, in individual cases many difficulties may arise in positively separating it from hyperparathyroidism[1178] A careful history will usually exclude the other causes of renal failure associated with either hypercalcemia or a compensatory hyperparathyroidism (i e , acute osteoporosis hypervitaminosis *D*, sarcoidosis, myelomatosis, and generalized carcinomatosis with osseous metastases)

Reference was previously made under Group III to the precipitation of hepatic coma and ammonium intoxication by the use of *ammonium resins, acetazoleamide* (Diamox) *methionine*, and *chlorothiazide* in the presence of severe liver disease (p 96)[350-352] The serious toxic effects of *ammonium chloride* in the presence of renal and hepatic disease have also been alluded to on several occasions (pp 96 and 251)[306]

A toxic nephrosis has been reported with *edathamil calcium disodium* (Versenate), the calcium chelate of ethylenediaminetetraacetic acid This compound is finding widespread use in heavy metal poisoning as a presumably nontoxic material[1172] Inasmuch as most physicians have only

infrequent occasion to use this or similar drugs, and inasmuch as the patients receiving such treatment frequently already have sufficient pathologic changes to account for divers renal, neurologic, cardiovascular, and hematologic abnormalities, many instances of toxicity due to these agents are probably either not recognized or not reported

Conscientious physicians must be cognizant of the possible erroneous basis on which a number of *agents for lowering the plasma lipids* (exclusive of a reduction in weight calories, and total ingested fat) are currently being administered on a wholesale basis in attempts to treat or prevent the atherosclerotic syndromes A direct relationship between the blood cholesterol levels and the development of human atherosclerosis has never been proved as an absolute fact notwithstanding the considerable body of evidence that would seem to support this assumption Contrary to current belief, it would appear that the cholesterol lowering effects of vegetable fats are not primarily related to their content of unsaturated fatty acids [285] Furthermore, the additional weight that follows the ingestion of these fatty substances may in itself prove to be harmful

Complications of Antibiotic Therapy

The current promotion of antibiotics is replete with misinformation and false claims Many statements and conclusions are indiscriminately set forth, being based on the inadequate data of short term pilot studies This is most notably apparent in the case of the newer antibiotics which are purported to be the 'drug of choice' in urinary tract infections The subsequent studies by careful workers inevitably disprove such unjustified advertising on the basis of resistance and reinfection but these reports unfortunately require months or even years to be forthcoming See also pages 112, 138, and 154

The statistical correlations between the use of the *sulfonamides* and the subsequent incidence of polyarteritis and 'allergic' vasculitis have been the object of much critical analysis during the past decade by both clinicians and pathologists (p 225) [819, 949] Whether similar long term complications will occur from the introduction of certain sulfonamide derivatives (Diamox the arylsulfonylureas) into everyday therapeutics remains to be seen

The Systemic Complications of Topical Dermatologic Therapy

The systemic complications of topical dermatologic therapy have received little attention even by the dermatologists It is not difficult to appreciate the pathogenesis of these disorders when one considers the following factors which enhance percutaneous absorption [47, 1188]

1 The high concentration and prolonged contact of the potentially toxic drugs that are often employed

2 The frequent warm soaks or baths taken by patients with generalized dermatoses prior to the topical applications

3 The rubbing utilized in applying most preparations

4 The relatively large cutaneous surface in children with respect to their body weight

5 The greater absorption of chemicals through the increased use of water-soluble vehicles as compared with the oleaginous vehicles

6 The markedly increased absorption (as demonstrated with phenol sulfonphthalein and tracer dyes) through inflamed skin, this being most pronounced in eczematous dermatitis

Since medical consultants are occasionally requested to evaluate complicated dermatologic problems, it is most pertinent within this text to enumerate and emphasize a number of these untoward effects

Boric Acid Intoxication

Solutions of boric acid are certainly safe in ordinary usage They become dangerous, however, with continued use in infants, or when they are applied to large areas of denuded skin The same consideration concerns certain popular brands of baby powder, the active ingredients of which are boric acid and talc In infants with boric acid intoxication, there is usually an intense erythema that may extend over the entire body The involvement of the palms and the soles gives an appearance reminiscent of acrodynia, particularly when accompanied by conjunctivitis and irritability In view of the striking similarity of this cutaneous reaction to the erythematous exfoliative dermatitis in the newborn and in young infants known as Ritter's disease, one wonders if many of the cases so described may not actually have been instances of boric acid poisoning Diarrhea, vomiting, and central nervous system signs suggestive of meningitis also occur

The presence of boric acid in the urine or spinal fluid can be rapidly confirmed by the turmeric paper test (p 700)[1185] or by quantitative colorimetric methods It is quite likely that the number of milder cases of boric acid intoxication which are not recognized is considerable [1186] It is also noted at this point that the best available therapy to date in severe cases of boric acid poisoning (provided irreversible tissue damage has not occurred) is by exchange transfusion [1187]

Salicylic Acid Poisoning

The characteristic syndrome of salicylate poisoning—respiratory, gastrointestinal, mental, and acid base disturbances—can be produced by the repeated inunctions of ointments containing this ingredient in high concentrations [1188] (Also see Group II page 65) Synthetic salicylic acid is currently utilized in the dermatologic therapy of many dermatoses for its antiparasitic, keratolytic, keratoplastic, anesthetic, antipruritic, and caustic effects

Phenol Poisoning

The significant blood levels of free and conjugated phenol that ensued when this substance was applied to large areas of the skin in a group of male volunteers—both in the form of phenol (2 per cent) in calamine

lotion, and in a liquid petrolatum base (Campho-phenique)—point out the potential dangers of such therapy[1189] The prominent features of phenyl salicylate (Salol) intoxication are also referable in part to its phenol content Chronic exposure to phenol may result in paresthesias, gastrointestinal disturbances, pruritus, renal and metabolic derangements and pigmentation of the skin A discoloration of the cartilages might even take place that closely resembles ochronosis

Mercurial Poisoning

Mercurialism has resulted from the use of ammoniated mercury in oleaginous and washable base vehicles As noted under Group II it has also followed the absorption of mercury containing powders used in detecting latent fingerprints (p 68)[47] One study relating to percutaneous absorption cites the case of a patient with generalized psoriasis who developed a mercurial stomatitis after being treated with ammoniated mercury[48]

Estrogenic Effects

Physicians should be cognizant of both the endometrial hyperplasia and the constitutional effects that can result from the percutaneous absorption of estrogenic substances in the form of cosmetic creams and lotions (These preparations can be readily purchased without prescription) Similar systemic effects may also occur in males who come in contact with solutions of high estrogenic potency, as in the case of biochemists processing pregnancy urine Genital atrophy, impotence, and gynecomastia have been reported in such instances[1190] It is of interest that after careful study of the subject by Behrman, the purported local advantages of estrogenic hormone creams applied to the facial skin over the regular use of a bland emollient cream were seriously questioned[1191]

"Broadening of the Allergic Base"

The fact that certain individuals, called atopics " are born with the capacity for becoming sensitized to a wide variety of external contactants as well as to inhaled and ingested substances is well appreciated This type of epidermal or dermal sensitivity is enhanced by the application of a host of other drugs (sulfathiazole, the 'caine compounds, penicillin, streptomycin nitrofuracin mercury the antihistaminics) when the individual is already allergic to one substance It must be suspected when a severe exacerbation of the patient s dermatitis follows this type of topical therapy[119] Furthermore an allergic type vasculitis may be noted in the blood vessels of tissues biopsied at sites considerably removed from the focus of sensitization It is a well known fact that the printer s ink has hardly been dry on a number of papers citing the virtues of a new non sensitizing topical preparation when case records of profound local and systemic reactions are inevitably reported

Exacerbation of Anhidrosis

The possibility of exacerbating the systemic manifestations of miliaria and anhidrosis (tropical asthenia, heat hyperpyrexia) as a result of the damage incurred by the use of irritating topical applications, soaps, detergents, or excessive bathing is cited further under Group XVII (p 528)

CONCLUDING REMARKS

The preceding remarks are concluded with the plea for clinicians, particularly "specialists," to maintain a constant and critical appreciation of the pharmacology and significant side effects of *every* potent drug they employ in *all* fields of therapeutics This is by no means intended to represent therapeutic nihilism Rather, if the patient's best interests are to be served, the practicing physician should not allow himself to be swayed too far from those techniques and regimens which have already proved valuable in his own hands This applies equally to the pressures being variously exerted upon him by drug brochures, films, detail men, isolated case reports, and even by the *avant garde* of the medical research world itself

The barrage of claims of *superiority* by drug houses of their particular antihistaminic preparations, vitamins, antispasmodics, tranquilizing agents, and antibiotics—the basic nature and actions of which are frequently essentially identical with several dozen others already on the market—has been increased in recent years The greatest hazard of this situation rests in the confusion and exhaustion it provokes in conscientious clinicians The ethics and untoward effects of such advertising have caused much concern in the minds of many physicians, especially since the Food and Drug Administration has but little recourse at present in these matters [116b]

Harrison and his colleagues have ably summarized *the scope of iatrogenic illness* in the following well chosen words, which are most appropriate in concluding this chapter

> But even if it were possible to finally achieve the goal—a generation of flawless physicians *with infallible judgment and infinite wisdom*—there would *still be the* patients who have uncanny capacity for misinterpreting the most innocent remarks and the most cautiously expressed opinions In the end iatrogenic illness is largely a matter of incomplete knowledge and fallacious judgment on the part of the *physician* conjoined with the fears and anxieties of the patient So long as medicine remains an art iatrogenic illness will remain The best hope for diminishing its incidence will come from a ceaseless consideration by the physician of the wisdom of each of his *decisions and* acts and from a greater appreciation of the mood and attitude of the person who consults the physician *

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GROUP XIV

Miscellaneous Entities, Including the Heredofamilial Disorders

PERIODIC DISEASE

IDIOPATHIC HEREDITARY LYMPHEDEMA

POLYOSTOTIC FIBROUS DYSPLASIA

PAGET'S DISEASE OF THE BONE

THE SICCA SYNDROME (SJOGREN MIKULICZ)

THE CONGENITAL AND HEREDOFAMILIAL DISORDERS

- *General Considerations*
    - Epigenetics The molecular concept of hereditary dise
    - Detection of the heterozygous state
- *Ectodermal Dysplasia and Its Variants*
- *Multiple Germ Plasm Dysplasia and Its Variants*
- *The Maffucci Syndrome*
- *Gargoylism*
- *The Laurence Moon Bardet Biedl Syndrome*
- *The Kartagener Syndrome*
- *The Turner Syndrome*
- *Myotonia Dystrophica*
- *Essential Renal Cystinuria*
- *Glycinuria*
- *Polycystic Disease of the Kidneys*
- *Medullary Cysts of the Kidneys*
- *Congenital Duplication in the Upper Urinary Tract*
- *Renal Agenesis*
- *Hereditary Hematuria Nephropathy and Deafness*
- *Cystic Disease of the Liver*
- *Intestinal Polyposis*
- *Arachnodactyly*
- *Incontinentia Pigmenti*
- *Osteogenesis Imperfecta*
- *Adenoma Sebaceum*
- *Tuberous Sclerosis*
- *Congenital Heart Disease and Asplenia*

Exacerbation of Anhidrosis

The possibility of exacerbating the systemic manifestations of miliaria and anhidrosis (tropical asthenia, heat hyperpyrexia) as a result of the damage incurred by the use of irritating topical applications soaps, detergents, or excessive bathing is cited further under Group XVII (p 528)

CONCLUDING REMARKS

The preceding remarks are concluded with the plea for clinicians, particularly "specialists," to maintain a constant and critical appreciation of the pharmacology and significant side effects of *every* potent drug they employ in *all* fields of therapeutics This is by no means intended to represent therapeutic nihilism Rather, if the patient's best interests are to be served, the practicing physician should not allow himself to be swayed too far *from those techniques and regimens which have already proved valuable* in his own hands This applies equally to the pressures being variously exerted upon him by drug brochures films, detail men, isolated case reports, and even by the *avant garde* of the medical research world itself

The barrage of claims of superiority by drug houses of their particular antihistaminic preparations, vitamins, antispasmodics, tranquilizing agents, and antibiotics—the basic nature and actions of which are frequently essentially identical with several dozen others already on the market—has been increased in recent years The greatest hazard of this situation rests in the confusion and exhaustion it provokes in conscientious clinicians The ethics and untoward effects of such advertising have caused much concern in the minds of many physicians, especially since the Food and Drug Administration has but little recourse at present in these matters [116 b]

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is not limited to this congenital disorder or to filariasis This feature may result from bacterial infection (elephantiasis nostras), syphilis, tuberculosis frambesia, lymphogranuloma venereum, neoplastic invasion, ulcerative colitis, and postoperative lymphatic occlusion [1 14a]

POLYOSTOTIC FIBROUS DYSPLASIA

The syndrome of polyostotic fibrous dysplasia is also known as Albright s syndrome and osteitis fibrosa *disseminata* In the classic form, the patient may literally resemble a pathological "curiosity shop" On the other hand, he may become the subject of intense diagnostic concern because, *for example of an asymptomatic bone lesion in one of this disorder's* many "formes frustes'

In the complete syndrome one encounters the following triad (1) a self limited disseminated osteitis fibrosa of both the hyperostotic and hypoostotic types, with the characteristic segmental distribution and "torn paper' appearance, (2) areas of very irregular light brown pigmentation which are also seen on either side of the midline particularly on the buttocl s sacrum, and upper spine, and (3) a true sexual and somatic precociousness in females, probably resulting from the associated hypothalamic irritation [1 16]

The cutaneous manifestations of the Albright syndrome are depicted in Figure 64 (Atlas page 40)

The cafe au lait pigmentation may also involve the mucous membranes Since these lesions contain excessive melanin they can closely simulate those seen in Addison s disease and in neurofibromatosis Other associated phenomena have included hyperthyroidism diabetes mellitus congenital arteriovenous aneurysms rudimentary l idneys atrophy of the optic nerve and mental deficiency In contrast to the osteitis fibrosa *generalisata* of hyperparathyroidism, the bone lesions are *not* true cysts and the serum electrolytes are usually normal

PAGET'S DISEASE OF THE BONE

Paget's disease of the bone (osteitis deformans) was previously mentioned in relation to the purported high incidence of fibrosarcoma and osteogenic sarcoma that complicate this condition in the older age groups (p 320) Occasionally great difficulty is encountered in differentiating it from metastatic disease to bone when only the pelvis, the skull or one of the long bones is involved In such an asymptomatic patient the demonstration of not only the lytic changes but also of new bone formation with bundles of irregular, trabeculated and widened bone an elevated serum alkaline phosphatase level (with a normal liver) and increased warmth of the skin overlying the lesion are usually diagnostic No bone of the body is immune to this disorder Even when extensive involvement is present, however there are always areas of normal and uninvolved bone to be found A previously elevated all aline phosphatase may fall if the patient with Paget's disease is immobilized

When a patient presents himself with degenerative arthritis of one

THIS SECTION, the title of which was chosen *faute de mieux*, is presented without apology for those clinicians who appreciate the importance of critically "browsing through the fine print" when confronted with perplexing chronic illness. From the study and interpolation of the pathophysiology which afflicts these unfortunates, it is possible to derive a more comprehensive and satisfying understanding of both the normal mechanisms with which *Homo sapiens* has been so magnificently endowed and the derangements of these mechanisms. Surely no one can deny that this is desirable for the physician, who within his limited realm, attempts to be "all things to all men" by the expedient of maintaining an open mind. Sooner or later, such study and insight will inevitably yield considerable diagnostic, prognostic, and therapeutic rewards.

PERIODIC DISEASE

Periodic disease and its many variants—including periodic fever, periodic peritonitis, periodic arthralgia, periodic edema, cyclic vomiting, recurrent parotitis, and periodic purpura—are well described in the recent literature, most notably by Reimann.[979, 1108, 1110] The relationship of cyclic thrombocytopenic purpura, edema, and cyclic neutropenia to the menstrual cycle, has also been the object of clinical interest.[1111, 11] Most episodes of periodic disease in women are independent of the menstrual cycle, however. Likewise a corresponding rhythm is not demonstrable in men.

From their observations dealing with periodic fever in the members of five generations of one family, Bouroncle and Doan have added further evidence to the belief that the trait is dependent upon a dominant, autosomal gene.[1209b] This disorder appears to be particularly prevalent in people of Armenian, Arabic, or Jewish extraction. Although the reaction is one of a recurrent, self-limited, and exudative rather than proliferative nature, *the clinical illness is not always benign*. *In view of the extreme ranges of* these manifestations, it is fortunate from the diagnostic standpoint that the episodes tend to be uniform in any given individual. The possibility of periodic fever being due to some other systemic condition (such as tuberculosis, polyarteritis, and malignant reticulosis) must always be kept in mind.

IDIOPATHIC HEREDITARY LYMPHEDEMA

Several features of idiopathic hereditary lymphedema (Milroy's disease) are not generally appreciated and can lead to diagnostic confusion. This condition may have its clinical onset not only shortly after birth but at any time between childhood and early adulthood. Among the series of reported cases, the frequent recurrent acute attacks *of pain, tenderness,* erysipelas-like or lymphangitic redness, fever, vomiting, and *malaise are* conspicuous—in addition to the lymphedema. Steroid *therapy may effect* a gratifying remission of these manifestations, but *accordingly cannot be used as a basis* for differentiating this disorder from the collagen disorders.[1, 13]

It is in order to recall that elephantiasis of the limbs or the genitalia

the parotid and other salivary glandular enlargement and the chronic polyarthritis (primarily seen in women over forty years of age) are definite components of this syndrome[1 0] They consider that this complex—heretofore ascribed to the vague Mikulicz disease—is usually a clinical and pathologic variant of the Sjogren syndrome

Sialography may aid in differentiating the *Mikulicz disease* (i e , the primary disorder which originates in the salivary gland) from the *Mikulicz syndrome* due to involvement of the adjacent lymphoid tissue by some systemic disease (i e leukemia, lymphoma tuberculosis sarcoidosis) (p 805)[1 0d] It is of added interest that the Sjogren Mikulicz syndrome has also been one of the predominant features in unusual cases of disseminated lupus erythematosus and amyloidosis[206]

An illustration of the Mikulicz syndrome appears in Figure 95 (Atlas page 62)

Rubin and Rubin have pointed out the diverse manners in which the Sjogren Mikulicz disease might present itself to a variety of specialists[1270d] These possibilities include the following the ophthalmologist—the sicca syndrome, the otologist—recurrent sialadenitis the internist—chronic rheumatic polyarteritis and the various dyscollagenoses, and the dentist—severe xerostomia Other features that are observed in the sicca disease include a hypochromic anemia altered glucose tolerance, alopecia, the Raynaud phenomenon caries scleroderma telangiectases, and a greatly accelerated sedimentation rate

Many clinicians are not aware of the frequency with which a sym metrical soft, nontender, and asymptomatic enlargement of the submaxillary glands occurs in individuals over the age of 50 years[320d] This entity is probably related to the chronic asymptomatic enlargement that can also affect the parotid glands (p 85) Its chief importance is the recognition of its benignity so that cancerophobia and unnecessary biopsies will be avoided

GENERAL CONSIDERATIONS RELATING TO THE HEREDOFAMILIAL SYNDROMES

The greater part of the rest of this chapter will deal with a number of congenital and familial disorders which are apt to be of considerable interest to clinicians who are actively engaged in a consultation practice The observations to follow repeatedly demonstrate that there is often a high yield of other congenital anomalies encountered should one be found, and the socioeconomic implications of such findings It has been shown for example that the incidence of congenital heart disease is five to tenfold greater in a group of blind or deaf children with relatively good mentality than in the general population Similarly of the many congenital cardiac malformations that are described as occurring in two or more members of one family patent ductus arteriosus recurs with the greatest frequency[1215]

Clinical facts such as the ones mentioned above further underscore *the great importance of a careful family history in solving a diagnostic problem* The hasty recording of negative family history" under these circum stances often removes the most significant single clue to the detection of

knee, it is wise to be sure he is not unknowingly favoring Paget's disease (or another lesion) involving the opposite tibia or femur Involvement of the maxilla is frequently first noted by dentists To one who is not familiar with the early stages of the skull involvement, the extreme degree of rarefaction affecting a considerable portion of the calvarium, known as *osteoporosis circumscripta*, can be most alarming While it is apparent that the dual diagnosis of Paget's disease of the bone and multiple myeloma in the same patient should be made only after considerable deliberation when there are specific indications for the coexistence of both disorders, several well documented reports of this combination have appeared [67 a]

It is also well to bear in mind certain *important and unique non malignant and nonorthopedic complications of Paget's disease of the bone* *A high output type of heart failure* may ensue, either with or without an underlying cardiac disorder This results from the arteriovenous shunt effect created by the osseous lesions, and the associated increase in local total blood flow (on occasion as much as twenty times the normal amount) (p 231) [1217] The marked thoracic deformities in this disease can also introduce the features of a cor pulmonale

The marked osteolysis often leads to hypercalciuria, *hypercalcemia*, and renal calculi, particularly if the patient is immobilized Nausea, vomiting, and dryness of the mouth should suggest the development of hypercalcemia Extensive arterial calcification, soft tissue calcification, and an increased incidence of cholelithiasis have also been noted

Several reports refer to an associated *lowered carbohydrate tolerance* and alimentary glucosuria These are attributed in part to the elevated serum alkaline phosphatase levels On the other hand, carefully performed oral and intravenous glucose tolerance tests (when corrected for age) have revealed essentially normal curves [1218]

A number of *neurologic manifestations* (headache, tinnitis, deafness, dizziness, and epileptiform seizures) may result from the impingement of the osseous pathologic process onto the cranial nerves and the brain Although considered somewhat of a rarity, compression of the spinal cord primarily as the result of Paget s disease has also been reported [1124] Relief has ensued following a decompression laminectomy

THE SICCA SYNDROME (SJOGREN MIKULICZ)

Another disorder whose systemic nature has been recognized only very recently, both clinically and pathologically, is the Sjogren or sicca syndrome It was previously considered to be merely an ophthalmologic or rhinologic entity, inasmuch as the major presenting symptoms and signs consisted of decreased or absent lacrimation, a dry filamentary keratitis and conjunctivitis and dryness or atrophy of the mucous membranes of the nose, throat, and mouth The simple litmus paper test for the "dry eye syndrome" (see Section XIII of Part II) may give the answer to such a prolonged foreign body sensation (p 809)

While Henderson denied that polyarthritis is an integral part of this disease in a review of the extensive experience at the Mayo Clinic [1219] Morgan and Castleman and others have re-emphasized the fact that both

We have only recently begun to appreciate the magnitude and the complexities incumbent upon any analysis of genetic pathology [1273] Each of man s 23 pairs of chromosomes probably contains as many as 5000 genes (It is conjectured that there are about 50,000 genes in man)[119e] These genes in turn, are subject to numerous variabilities in expression either individually or in chains Many of the previous theories relating to dominance and recessivity, the prenatal and postnatal influence of environment, the single gene basis of hereditary syndromes (genuine pleiotropism) and the "absence' of enzymes concerned with either intermediate metabolism or specific functional processes will undoubtedly require modification as greater insight is achieved by geneticists investigators in the basic sciences and clinicians (One of the most significant discoveries relating to the mechanisms of heredity has been the demonstration that desoxyribonucleic acid (DNA) is not only contained wholly within the chromosomes of the nuclei of cells, but that the wavelengths of ultraviolet radiation which can induce experimental mutations correspond to the absorption spectrum of DNA)

The relative responsibilities of both genetic and environmental influences are beginning to be understood more clearly in a host of important disorders In the cases of coronary artery disease hypertension rheumatic fever, and diabetes mellitus, for example, such factual data might bear considerable fruit When the close relationship between genes and protein synthesis is regarded in light of the 100 000 or more different proteins in the human body, one realizes the limited extent of our current basic comprehension of genetic derangements

The importance of the ever increasing problem of genetic mutation and the potentiation of latent recessive traits following ionizing radiation received attention in the preceding chapter (p 397) When mutations do occur they usually do not show up in the first generation, in fact they may not become manifest for ten or more generations [1193e]

Many hereditary disorders are not congenital (i e , apparent at birth), but require years of aging and exposure of their unique hereditary substrate to environmental factors and stresses before their clinical expressions become manifest This is best exemplified by diabetes mellitus, various allergic states and a number of dermatologic entities, such as xanthoma tuberosum and neurofibromatosis In neurofibromatosis, the gene is fully penetrant (that is there will ultimately be some abnormality noted in everyone who harbors it) Sorsby has emphasized in his fine book on "Clinical Genetics that man because his families are small leaves much to be desired as an animal for genetic study since genetics is a statistical science [1272b]

The clinician and consultant must accordingly be constantly aware of the fact that *up to half of the population probably possesses a gene for some hereditary disease* which in many instances may actually be accounting for considerable minor morbidity In certain disorders such as diabetes mellitus and familial polyposis of the large bowel it can be controlled once recognized The studies of asymptomatic individuals with radioactive iodine and radiocobalt labeled vitamin B_1 among the relatives of patients with thyrotoxicosis and pernicious anemia respectively have conclusively verified the familial diathesis in these particular diseases [1]

a hereditary syndrome It is a sobering truism that the advent of the antibiotics and other life-saving measures which have kept genetically inferior individuals alive has also served to enhance the magnitude of the genetic diseases by enabling these individuals to procreate In spite of its relative importance, information concerning the health of grandparents is rarely sought or recorded when a possible familial disorder is encountered clinically, such as in instances of leukemia[664] and unexplained cardiomegaly[830]

There still exists considerable confusion concerning the term "congenital" as it is variously used with reference to truly inherited defects and to those which are acquired *in utero* This issue is best exemplified in the case of congenital heart disease, wherein the designation of "antenatal" is probably preferable when allusion is being made to both groups[1.15] It is of further interest in this regard that individual siblings may demonstrate diverse syndromes stemming from multiple genetic defects, such as the Turner syndrome in one and the Laurence-Moon Biedl syndrome in an other[1233b]

These conditions also point out the increasing importance of *epigenetics* (i e , the study of how a gene produces its effects in the individual) and the *molecular concept of hereditary disease* (i e , abnormalities in the *genes being reflected by abnormalities in the molecules formed*)[1.21] The striking pathologic effects of the various "epigenes" when hemoglobin and certain enzymes are the molecules affected have already been set forth in discussions of the sickle cell variants, the specific plasma protein defects (viz , hemophilia, afibrinogenemia, agammaglobulinemia Wilson's disease) and the many "inborn errors of metabolism"

Clinicians must be cognizant of the fact that many more individuals carry these "epigenes" than just those few who are afflicted with the homozygous form of a given disease The frequency of *heterozygous carriers in the population* is estimated at about twice the square root of the clinical incidence of any hereditary condition For example, although only one in forty thousand people have clinically apparent phenylketonuria, about one individual in every one hundred probably carries one gene for this rarely seen disorder

A recent and very readable text by Sheldon Reed entitled, "Counseling in Medical Genetics" clearly defines the general and specific issues of this subject[12] The potentiation of previously concealed deleterious mutations by consanguinity in such conditions as all aptonuria, xeroderma pigmentosa and congenital ichthyosis is concisely set forth The significance of the ubiquitous heterozygote (the "common carrier") is further enforced by a consideration of the following incidences of homozygotes in any given disorder and of their respective heterozygous carriers (according to the Hardy-Weinberg Law)

Frequency of Patients	*Frequency of Carriers*
1 in 10	1 in 2.3
1 in 100	1 in 5.6
1 in 1 000	1 in 16
1 in 10 000	1 in 51
1 in 100 000	1 in 159
1 in 1 000 000	1 in 501

phenylketonuria galactosemia, cystinuria, and porphyria For example it is relatively easy to detect the asymptomatic homozygous relative of a patient with cystinuria or aminoaciduria of other types With this information, one can institute simple prophylactic measures (viz, dietary restrictions, the use of alkalis, and an increase in the volume of urine flow) that may obviate the subsequent development of renal calculi (*vide infra*)[1, 68]

The Germinal Dysplasias

Reference was made to the various syndromes resulting from single or multiple germinal dysplasias under the subject of the neurodermatoses (p 382) The neurodermatoses represent but one type of ectodermal dysplasia In ectodermal dysplasia of the anhydrotic type (Widderburn) and the hydrotic type (McKay Davidson) the defect is also restricted to the ectodermal germ layer, while in the syndromes of Rothmund Thomson and Werner, the sequelae of multiple germ plasm defects are present[1, 7, 12, 9] It is emphasized that these conditions are *not* primary endocrinopathies On occasion, striking hereditary stigmata have plagued these 'clinical experiments of nature"

The *congenital ectodermal defect* may be characterized by hypotrichosis absence of the sweat and sebaceous glands adontia or hypodontia, absence or malformation of the nails a characteristic facies, and even absence of the mammary glands[196] None of these patients demonstrate cataracts Their skin is usually smooth and fine The poor development of the jaw and the maxilla subsequent to the defective dentition results in a unique expression that consists of thick lips (a compensatory response) sunken cheeks, and a pointed chin Furthermore, there may be a so-called saddle nose in the congenital ectodermal defect that is induced by the local bony destruction from the chronic rhinitis Females are rarely subject to the dominant form of this disorder

The cutaneous manifestations of congenital ectodermal defect are depicted in Figure 91 (Atlas page 59)

As noted in Group IV ectodermal dysplasia can present itself as obscure fever (p 106)[374] Although mental deficiency is occasionally present, most of these patients have a normal mentality (presumably because the anlage of the nervous system became distinct from the cutaneous ectoderm long before the apparent injury during the third month of intrauterine life)

In the *multiple germ plasm dysplasias* one finds numerous classic and formes frustes" variations among the separate entities Various bones are shortened and deformed in these dysplasias most notably the tibiae, fibulae, radii ulnae and the tubular bones of the hands and feet Polydactyly or syndactyly may also be present

The following characteristics of *Werner s syndrome* are presented as a prototype shortness of stature premature graying of the hair premature baldness scleropoikiloderma, trophic ulcers of the legs, hyperkeratosis of the feet juvenile cataracts with starlike opacities, hypogonadism, diabetes mellitus calcification of blood vessels, osteoporosis, and metastatic calcifications[1, 7]

In *Rothmund s syndrome,* the cataracts and telangiectasia appear

Women who repeatedly bear markedly overweight babies may be merely manifesting a specific underlying genetic trait for this characteristic or a relationship to obesity that is unrelated to the "anticipation of diabetes Nevertheless, this phenomenon must always be regarded as a possible prediabetic state This is all the more important if there is a diabetic family history Even among the leukemias, lymphomas, and other neoplastic diseases, striking instances of multiple siblings being so afflicted continue to be reported in increasing numbers [664]

The *relationship of the blood types to disease* poses a source of continuing interest, but still remains a most inconclusive subject For example, *several analyses involving large groups of both patients and controls* have resulted in the conclusion that there is up to a 35 per cent higher incidence of blood Group A types in patients with pernicious anemia or gastric cancer [1224a] However, Wiener and Wexler have wisely re-emphasized the potential technical fallacies and pitfalls in any such attempted association between *the blood groups and specific disease processes* [1 4b]

As knowledge accrues concerning these genetic disorders, more accurate *methods for the detection of their carrier states* will be presented to the clinician Several currently available examples include the specific gravity test (p 721), the l-phenylalanine tolerance test (p 369), urinary porphyrin determinations (p 703), and the vascular studies on the bulbar conjunctiva (p 808) to be used in detecting carriers or individuals with latent diabetes insipidus, phenylketonuria, porphyria, and diabetes mellitus, respectively Similarly, studies of the serum lipids can uncover the abnormal heterozygous states of essential familial hypercholesterolemia and familial hyperlipemia The fat tolerance test is particularly helpful in the latter instance (pp 78 and 827) [283]

The routine study of Negro Air Force personnel by means of the paper hemoglobin electrophoretic techniques (pp 196 and 682)[716 718] demonstrates the value of detecting a latent pathologic genetic state, since the avoidance of high altitudes by individuals shown to harbor the sickle cell hemoglobin C trait will usually prevent serious splenic infarction which could occur during flight [723]

The possible hypersusceptibility or hyposusceptibility of certain individuals and families either to disease states or to drug reactions on the basis of a latent genetic trait or enzyme deficiency was discussed in an *earlier chapter (p 63)*

The extraordinary diversity of congenital (and usually hereditary) defects as they can affect one organ is shown in the case of the kidneys The inborn functional abnormalities of the specific tubular systems can induce a variety of distinct syndromes These include nephrogenic diabetes insipidus, renal glucosuria, renal glucosuria with aminoaciduria essential cystinuria, cystinosis (the Fanconi syndrome) and renal tubular acidosis [1780]

Finally, one needs only to recall the recent revolutionary therapeutic approaches in the form of dietary management and drug therapy, that have rendered many disorders either curable or treatable, to be imbued with the importance of maintaining a continuing *interest in hereditary* syndromes, however rarely they are encountered These syndromes include

Gargoylism

Some fundamental information pertaining to gargoylism (the Hunter Hurler disease, dysostosis multiplex) has appeared recently Individuals with this condition exhibit many unusual physical skeletal, ocular, auditory, hematologic, visceral, endocrine and cutaneous features Characteristically the patient presents with dwarfism, a large asymmetrical skull, kyphosis, splenomegaly, hepatomegaly, corneal clouding, narrow palpebral fissures hernia, deafness and a myxedematous type of skin

Gargoylism is depicted in Figure 93 (Atlas page 61)

The cardiomegaly and changes in the heart were described in a previous chapter (p 235) Bone studies usually reveal retardation of growth with lacking tubulation of the bone shafts loss of the normal trabeculation, and an unusual degree of cartilage growth and bone formation at the epiphysiometaphyseal junction The reader is referred to the papers by Cole, Smith, and Caffey for their fine reviews and discussions [1-32] McKusick has clearly shown that the disorder stems from the distention of the cells with a complex polysaccharide and an aglycolipid and that the fundamental defect concerns the structural polysaccharide of connective tissue [1232d]

Laurence Moon Bardet Biedl Syndrome

The Laurence-Moon Bardet Biedl syndrome is one of the better known combinations of multiple congenital anomalies The five main features include retinitis pigmentosa obesity mental retardation, polydactylism and hypogenitalism Other defects of a skeletal, neuromuscular or cardiac nature may also be noted on occasion [1233] Another hereditary disorder that can be associated with retinitis pigmentosa is the Fanconi syndrome [195b]

Kartagener Syndrome

The triad of situs inversus (complete or incomplete), bronchiectasis, and chronic sinusitis or sinus hypoplasia constitutes the equally well known Kartagener syndrome It is probable that atelectasis precedes the bronchiectatic lesion even though the congenital factor seems to be fairly well established [1234]

Turner Syndrome

The association of multiple congenital anomalies (particularly webbing and shortening of the neck cubitus valgus various ocular abnormalities a shield chest, and coarctation of the aorta) with primary ovarian agenesis or arrest constitutes the Turner syndrome This entity was previously discussed with the endocrinopathies (p 36) [1 6 127]

Myotonia Dystrophica

Myotonia dystrophica (or myotonia atrophica) is a hereditary disease that usually becomes manifest in middle or late life It is characterized by marked myotonia, a progressive frontal alopecia at an early age the wast

earlier in life (i e , between three months to six years) The skin is generally thin and pliable with no ulcerations[1227a]

Children who have *progeria with nanism* (Hutchinson Guilford) are dwarfed, sexually retarded, and have but little hair Their skin is taut and atrophic They exhibit premature senile changes and usually die before the third decade No familial tendency, pressure ulcers, or cataracts are usually encountered[1230]

The cutaneous manifestations of progeria are depicted in Figure 94 (Atlas page 61)

Other Congenital and Familial Syndromes

The following is a brief list of some of the more important hereditary disorders that have already been discussed in this book

Wilson s hepatolenticular degeneration (p 100)
Diabetes mellitus (p 69)
Galactosemia (p 75)
Hemochromatosis (p 60)
Porphyria (p 61)
Osler Weber telangiectasia (p 222)
The neurodermatoses (p 382)
The Fanconi syndrome and other variants of cystinuria (p 57)
The various hereditary anemias (pp 190–197)
The Ehlers Danlos syndrome (p 314)
Nonendemic familial cretinism with goiter (p 17)
Pernicious anemia (p 190)
Thyrotoxicosis (p 18)
Diabetes insipidus (p 33)
Nephrogenic diabetes insipidus (p 33)
The disorders of lipid metabolism (p 76)
Phenylketonuria (p 369)
Rheumatic fever (p 310)
Familial cardiomegaly (p 416)
Nephrosis (p 55)
Glycogenosis of the heart (p 76)
Pulmonary alveolar microlithiasis (p 128)
Fibrocystic disease of the pancreas (p 48)
Chronic relapsing pancreatitis (p 48)
Periodic disease (p 412)
Gout (p 74)
Ochronosis (p 75)
Amyloidosis (p 60)
Hypophosphatasia (p 26)

Maffucci's Syndrome

The curious association of the vascular hemangiomata (viz , angioma phlebectasia, and hamartoma) with the devastating deformities of dys chondroplasia are included under the title of *Maffucci's syndrome* This inborn dysplastic mesodermal anomaly was recently reviewed by Bean[1231] Its significance lies in the very high incidence of associated malignant neoplasms The latter have included chondrosarcoma, angiosarcoma malig nant lymphangioma, glioma, and ovarian teratoma The angiomas of the skin may be associated with *an asymmetric hemangiectatic hypertrophy* of the limbs and multiple gastrointestinal or peritoneal vascular anomalies

with congenital aneurysms of the cerebral vessels, but also with aneurysms of the carotid artery, the coronary artery the abdominal aorta, and even dissecting aneurysms of the thoracic aorta [1 41b] Furthermore numerous defects in the central nervous system, the genitourinary system, the gastrointestinal tract, and the extremities can be encountered in the younger age groups Aberrant biliary cysts of the liver and pancreatic cysts are occasionally found in adults

Medullary Cysts of the Kidneys

Medullary cysts of the kidneys is a condition characterized by many little cysts within small and contracted kidneys Clinically, it is associated with insidious uremia and anemia [24] The retinal and cardiac changes are usually minimal Reference was previously made to the salt-losing syn drome associated with these kidneys, producing a state that can closely simulate adrenocortical insufficiency (p 15) Since cysts in both the liver and the pancreas are encountered at times—as they are in the classic form of polycystic kidney disease—it is not unlikely that this condition will ultimately be found to represent an unusual variant of the latter entity

Congenital Duplication in the Upper Urinary Tract

The discovery of some congenital duplication in the upper urinary tract (double kidney pelvis and ureter) merits a search for similar malformations in close relatives This poses a potentially serious problem for two reasons First such lesions represent the commonest type of urinary tract anomalies and secondly the anomalous kidney is twenty times more prone to pathologic complications than a normal kidney (due to the high frequency of associated obstructive defects) [1242]

Renal Agenesis

A similar implication applies in the case of renal agenesis [1 43, 1 44] Every patient so affected must be made aware of this fact promptly in order to avert the subsequent catastrophe resulting from an ill advised nephrectomy The occurrence of hematuria following minimal trauma to the renal area in children should alert one to the possible presence of a congenital uropathy This is particularly true with reference to the hydronephrosis secondary to a congenital obstruction at the ureteropelvic junction [1245a] In the younger patient with enuresis dysuria or abdominal colic, another clue to the possible presence of renal agenesis or some other congenital genitourinary malformation is the finding of a gross ear deformity [1.45b]

Hereditary Hematuria Nephropathy and Deafness

Reyersbach and Butler and Sturtz and Burke have called attention to their unique experiences with a number of patients exhibiting hereditary hematuria nephropathy, and deafness [1246] All ages are represented in this

ing of the muscles (particularly the sternocleidomastoids), gastrointestinal disorders with spruelike manifestations, and various types of lens opacities[1235] Testicular atrophy with preservation of the interstitial cells or ovarian deficiency are found in 80 per cent of the cases[1 37] (Cases of ovarain agenesis and the Klinefelter *syndrome have also been noted in families* afflicted with amyotonia congenita (Oppenheim's disease) and infantile cataract[128])

This dystrophic process often affects the myocardium in the form of cardiomegaly and can cause electrocardiographic changes[1238] The condition differs from the more benign myotonia congenita (Thomsen's disease) which is much rarer and lacks the aforementioned dystrophic features

Essential Renal Cystinuria

The hereditary renal tubular defect in essential renal cystinuria not only involves the reabsorption of cystine, but also that of lysine, arginine, and ornithine[178c, 1 26b] Inasmuch as cystine crystals do not form in all cases of cystinuria, the incidence of this disorder is undoubtedly much higher than would be indicated merely by the frequency of cystine stone formation Since cystine is much more soluble in alkaline urine than in the physiologic pH of urine, crystallization of this amino acid can be minimized by the ingestion of alkalinizing salts and increased amounts of fluids[1 6] The relative benignity of this disorder contrasts markedly with the gravity of cystine storage disease or cystinosis (p 57)

Glycinuria

The technique of paper chromatography, by which specific patterns of urinary amino acid excretion can be determined, has cast light on a number of other previously unsuspected hereditary disorders Glycinuria is another such aminoaciduria It may be associated with recurrent bilateral nephrolithiasis This disorder differs from cystinuria in that it is apparently much rarer, it is associated with a dominant pattern of inheritance, and the urinary stones are composed chiefly of oxalate rather than glycine[1226e] The failure to reabsorb glycine is not associated with defective reabsorption of either the other amino acids or of phosphate or glucose

Polycystic Disease of the Kidneys

A number of significant congenital anomalies may be associated with polycystic disease of the kidneys This suggests that the polycystic disease often represents but one phase of a multifaceted congenital disorder, somewhat analogous to the situation in tuberous sclerosis, neurofibromatosis, and the von Hippel-Lindau disease Intracranial "berry" aneurysms and coarctation of the aorta are observed relatively commonly in association with this renal anomaly[1 40, 1241] The symptom of headache or the occurrence of a cerebrovascular accident in such a patient accordingly merits prompt and intensive investigation

Polycystic disease of the kidney and liver has not only been associated

the patient suffering from periodic abdominal pain, recurrent intussusception and unexplained anemia or melena Alopecia and atrophy of the fingernails and toenails are other features of this entity [125] Isolated instances of urinary, bronchial, and nasal polyps retarded development, and thyroid, adrenal, and ovarian disease are on record in association with the classic features of the Peutz Jeghers syndrome [1 50b]

Other growth abnormalities might similarly alert the clinician to the presence of *associated adenomatosis of the bowel* These include sebocystomatosis, fibromas, fibrosarcomas, and leiomyomas The latter have been encountered in subcutaneous mesenteric, and retroperitoneal locations [1009]

Arachnodactyly

Arachnodactyly (Marfan s syndrome) has recently emerged from its obscurity in the recesses of the pathological and ophthalmological files to assume considerable clinical significance Aside from the subluxation of the lens and the bony abnormalities of the head, chest, and spine, there is a high incidence of associated congenital cardiac defects and cystic necrosis of the media of the aorta [878] The latter may result in pronounced aortic insufficiency and dissecting aneurysms, particularly after traumatic accidents [1 53 1 56] The first intimation of the presence of Marfan s syndrome may be the finding of cardiac enlargement murmurs and most significantly the demonstration of an aneurysmal dilatation of the aortic sinuses [901d] This observation assumes some importance when it is realized that the classic stigmata of this syndrome might not be apparent in infancy and childhood

Arachnodactyly is depicted in Figure 90 (Atlas page 58)

Several of these patients have been subject to repeated pneumothorax presumably due to the defective ground substance in the lung The familial incidence may be strong It should be noted that arachnodactyly like fingers capable of hyperextension are also observed in patients with sickle cell disease and pheochromocytoma [1358] Other characteristics that may be found with frequent repetition in kinships who are afflicted by the Marfan syndrome include multiple hernias hypermobility of the joints, a high arched palate pectus excavatum (funnel breast') pectus carinatum ('pigeon breast), dolichocephaly and kyphoscoliosis [1 54]

Incontinentia Pigmenti

Incontinentia pigmenti is one of the cutaneous manifestations of a congenital and possibly familial disorder which affects various structures of ectodermal and mesodermal origin including the autonomic nervous system [1257 1 58] There is a striking and bizarre arrangement of pigmented macules in chocolate-brown designs including whorls patches, and spidery forms Alopecia delayed dentition osseous deformities, corneal opacities cataracts, and a variety of neurologic phenomena (spastic paralysis, strabismus epilepsy microcephaly mental deficiency, optic atrophy) have been observed

syndrome, which includes hematuria, cylindruria, albuminuria, normal kidney function (usually), nerve deafness, and congenital abnormalities of the eyes (in some cases) Others have also noted these striking combinations of anomalies affecting family trees in which chronic renal disease, spherophakia, congenital cataracts, and inner ear deafness are associated [1,47] Since exacerbations of the hematuria can occur either spontaneously or with infection, and since there is an increased tendency to toxemia of pregnancy, difficulty may be encountered in differentiating this benign disorder from acute and chronic glomerulonephritis

Nonparasitic Cystic Disease of the Liver

The finding of nonparasitic cystic disease of the liver should similarly alert the clinician not only to cystic involvement of other organs (particularly the kidneys, the lungs, and the pancreas), but also to the possibility of additional congenital anomalies The latter include diverticula in various portions of the gastrointestinal tract and aneurysms of the cerebral vessels [1,43] The diagnosis has been accurately made by peritoneoscopic examination [1249] The incidence of this disorder is significantly associated with that of both benign and malignant neoplasms

Intestinal Polyposis

Intestinal polyposis is an integral feature of several familial syndromes The high incidence of malignant degeneration in these lesions is universally appreciated These associated counterparts of otherwise seemingly trivial syndromes must therefore be regarded as important because they can direct the attention of the observant clinician towards asymptomatic bowel neoplasms

The cutaneous manifestations in these disorders include an interesting spotty melanin pigmentation of the lips palate, cheeks, gums, digits, and other areas of the skin (p 514) [1,50] This periorificial pigmentation consists of level, dark brown or black macules While they may fade or even disappear about puberty, they tend to persist on the lips, the buccal mucosa, the gums, and the palate throughout life One can readily appreciate the difficulties that might occasionally arise in distinguishing the oral pigmentation in this disorder from that encountered in Addison s disease, pernicious anemia, sprue, and Whipple's disease No general darkening of the skin or mucous membranes is described in the Peutz Jeghers syndrome, however

The cutaneous manifestations of the Puetz Jeghers syndrome are depicted in Figure 2 (Atlas page 3)

Osteomatosis (leontiasis ossea), in which multiple osteomas are found arising from those bones which are predominantly preformed in membranes, is occasionally also observed as a concomitant clinical variant of intestinal polyposis [1,1]

It is emphasized that in the condition of intestinal polyps and melanin pigmentation—often referred to as the *Peutz Jeghers syndrome*—the polyposis not only affects the large bowel but also the small intestine, particularly the jejunum This diagnosis should accordingly be carefully considered in

dition when congenital cardiac anomalies are found in association with a leukocytosis and an unusual blood picture (p 189) [54]

The gravity of the malformations of the heart or great vessels is emphasized by the fact that only 4 of 80 patients with this syndrome lived beyond the age of three years In view of the frequent association of defects involving the conotruncal septum and the atrioventricular endocardial cushions with the asplenia, it is suggested that the noxious antenatal factor occurred as the anlage of the spleen arose simultaneously with the elaboration of the cardiac jelly The multiplicity of serious anomalies of the heart and great arteries in association with the anomalous systemic venous return and common mixing chambers usually precludes definitive benefit from surgery [54] (None of the cases reported have had the classic tetralogy of Fallot)

The finding of polycythemia and numerous Howell Jolly bodies in an infant with congenital heart disease is almost pathognomonic of this combination of anomalies The demonstration of another specific type of erythrocytic inclusions known as Heinz bodies is also highly suggestive of asplenia (if toxic factors are excluded) but requires special staining (p 673)

There is also a unique tendency among these patients to exhibit visceral symmetry This is suggested by the frequent finding of such features as three lobes in each lung, a large symmetric liver persistence of the dorsal mesentery to the duodenum and colon, an anatomic or functional two-chambered heart, and the cited absence of the spleen (which actually is the only unilateral mesenchymal organ in the body)

Osteogenesis Imperfecta

Osteogenesis imperfecta (fragilitas ossium) is another clinically significant, *mendelian dominant, non sex linked disorder* It is characterized by a decrease of osteoblastic activity which results in the imperfect formation and calcification of periosteal and endochondral bone Even though the bones may appear relatively normal (both in size and in calcium content) in the so called adult form of the disease, they are still prone to fracture after minimal trauma

Otosclerosis with conduction deafness (and to a lesser degree, nerve deafness) and blue sclerae are other components of this syndrome, but need not always be present (The latter sign is due to the choroid vessels and choroid pigment showing through the very thin sclerae) There is no correlation between the number of fractures and the presence or absence of blue sclerae [159] The extensive disturbance in the other tissues of mesenchymal origin is manifested by the great pliability of the blood vessels, fascia, periosteum, and subcutaneous tissues, and by the abnormalities of platelet function

Adenoma Sebaceum and Tuberous Sclerosis

Adenoma sebaceum is a congenital and often familial disorder in which a variety of neoplasms are frequently found The latter include rhabdomyomas of the heart and kidney tumors The sebaceous glandular involvement in this nevoid disorder is manifested early in life by the *appearance of firm, yellowish, waxy papules over the middle third of the* face on the inner cheeks and nose One may also find concomitant telangiectasia (in the so-called Pringle type), dystrophy of the nails, and small subungual fibromas of the fingers and toes [1385]

Mental retardation epilepsy, multiple intracranial calcifications, and adenoma sebaceum, plus a variety of dermatologic lesions characterize *tuberous sclerosis* (Bourneville-Pringle's disease, epiloia) Another feature of this disorder is the pulmonary involvement Chronic progressive dyspnea, recurrent pneumothorax, hemoptysis, cough, and diffuse miliary or small cystic changes in the chest films (resembling the "honeycomb" lungs of xanthomatosis) are frequent [160] Infection tends to be either absent or late in its development

The appearance of adenoma sebaceum in tuberous sclerosis is illustrated in Figure 67 (Atlas page 42)

Various osseous abnormalities are also noted in tuberous sclerosis, most commonly affecting the hands, the metatarsals, and the skull These changes include sclerosis, periosteal thickening, rarefaction, and cyst formation

Congenital Heart Disease and Asplenia

The syndrome of congenital heart disease and asplenia *is rare* It is nevertheless being encountered with increasing frequency in the literature (a total of 93 cases having been reported to date) *because of the important* therapeutic and prognostic implications involved Reference was made in an earlier chapter to the possible misdiagnosis of endocarditis in this con

RENAL COMPLICATIONS

Chronic nephritis and uremia Pyelonephritis and necrotizing renal papillitis Acute tubular necrosis (necrotizing nephrosis) Acute renal failure in pregnancy Nephrectomy of a sole functioning kidney Renal tract complications of prostatism and prostatic surgery Urinary extravasation Atheromatous emboli to the kidneys after aortic surgery

HEMATOLOGIC COMPLICATIONS

Transfusion reactions The problem of contaminated blood Citric acid intoxication Hyperheparinemia, with or without thrombasthenia Fibrinolysis Postsplenectomy thrombocytosis Other considerations relating to splenectomy and thrombocytopenia Postoperative anemias

HEPATIC COMPLICATIONS

Jaundice Homologous serum hepatitis Pylephlebitis Unrecognized liver disease Elevated blood ammonia levels following portacaval shunts

INFECTIOUS COMPLICATIONS

Evaluation of a high postoperative fever Vascular collapse due to infection Staphylococcal infections Tetanus Salmonella enteritis Malaria Tuberculosis Meningitis following spinal anesthesia *Clostridium welchii* sepsis Post splenectomy infectious diathesis Other infections in the postoperative period

ENDOCRINE COMPLICATIONS

Pheochromocytoma Adrenocortical insufficiency Postoperative diabetes insipidus Hypothyroidism Postoperative hypoparathyroidism Other complications of thyroidectomy Persistence of hyperinsulinism Parathyroidectomy failures

COMPLICATIONS OF DRUG THERAPY

Allergic reactions Excessive or aberrant response to drugs Hypotensive and other cardiovascular effects of drug therapy Withdrawal syndromes

DERANGEMENTS IN NUTRITION BODY FLUIDS, AND ELECTROLYTES

Postresectional nutritional derangements Hypoproteinemia and malnutrition Diabetes mellitus Hypoglycemia Postoperative hypovolemia Iatrogenic heatstroke Dehydration and fever Dehydration resulting from prolonged nasogastric tube feeding Hypodermoclysis-induced complications General comments relating to specific postoperative electrolyte derangements Hyponatremia Hypokalemia Magnesium deficiency Excessive diuresis Overhydration Hyperchloremic acidosis and hypokalemia following ureterosigmoidostomy Excessive salt administration Ammonium intoxication following portacaval shunts Hypernatremia

GROUP XV

Obscure Postoperative Complications

CARDIAC COMPLICATIONS

Postoperative myocardial infarction Aortic stenosis Heart strain and failure The pregnant patient with rheumatic heart disease Disorders of rate and rhythm Cardiac *arrest during and after surgery* *Postoperative pericarditis* Hemopericardium and pericardial tamponade Failure of surgery for constrictive pericarditis Other causes of electrocardiographic abnormalities The postcardiotomy *syndrome* *Postoperative endocarditis* *Undiagnosed multivalvular disease* "Recurrent mitral stenosis" Problems attendant upon open cardiac surgery and the use of extracorporeal perfusion Surgical and anesthetic problems unique to Negroes

VASCULAR COMPLICATIONS

Phlebothrombosis, with or without embolism or phlebitis Fat embolism Atheromatous emboli to the kidneys after aortic surgery Air embolism Complications of induced hypothermia Complications of induced hypotension

PULMONARY, PLEURAL, AND PULMONOCARDIAC COMPLICATIONS

Pulmonary embolism Pneumonitis, with or without atelectasis Aspiration as a complication Respiratory insufficiency Carbon dioxide narcosis Pulmonocardiac failure Pulmonary hypertension Pneumothorax Subcutaneous and mediastinal emphysema Activation or spread of pulmonary tuberculosis Bronchopleural fistula Residual stump disease Thoracoplasty failures and complications Unusual complications following thoracoplasty or lobectomy Pendular motion of the mediastinum *Paradoxical motion* of the chest wall Rupture of the esophagus Anesthetic problems, with particular reference to the presence of extensive pulmonary disease Tracheitis sicca Retropleural hematomas following sympathectomy *Severe intrathoracic* hemorrhage associated with thoracotomy Radiation pneumonitis

usually give no difficulty in diagnosis are omitted Mention is also made of the occasional obstetric problem case that arises for which the advice of an internist is sought either before, during or after delivery The many subtle medical considerations encountered by anesthetists that determine both the choice of anesthetic agents and technique of administering them will be briefly alluded to in the appropriate sections Less attention will be devoted to surgical techniques *per se*, even though they may actually have considerable bearing upon complications (such as the isolation of the pulmonary artery, the technique of pulmonary re expansion, and the proper closure of the bronchus)

Internists and chest physicians are being called upon with increasing frequency to evaluate obscure cardiovascular and pulmonary complications following general and thoracic surgery The reasons for such an emphasis can readily be appreciated in light of the constantly widening scope of these fields, with the creation of newer problems in both diagnosis and therapy for the nonsurgical consultant For example, one needs only to recall the increasing number of procedures now being performed on the heart, lungs, and great vessels, the success in preparing and maintaining individuals in the older age groups through major surgery and the development of newer anesthetic agents and techniques (hypothermia induced hypotension, pump oxygenators and open heart surgery) which have rendered many of these operations feasible within the last few years

In some instances the unique manifestations of otherwise readily defined disorders may be confusing This is exemplified by the clinical variability of myocardial infarction congestive failure or pulmonary embolism occurring postoperatively On the other hand certain complications have been introduced which were not previously encountered Among the latter might be cited the postcardiotomy syndrome postcommissurotomy endocarditis, and the sequelae of induced hypothermia and induced hypotension

CARDIAC COMPLICATIONS

Postoperative Myocardial Infarction The usual clinical manifestations of myocardial infarction are ob erved in only 50 per cent of patients who develop this condition postoperatively with pain being present in only one third of the cases[1263] Persistent hypotension is a very important and frequent clue heart failure and dyspnea may also occur These features are *even more significant in the presence of gout diabetes mellitus obesity*, previous hypertension, xanthomatosis and polycythemia—each of which predisposes to coronary disease In the series of 25 cases of postoperative myocardial infarction presented by Wasserman, Bellet and Saichek this complication occurred within the first seven days in 23[1 63a]

As a result of the increased awareness of the incidence of postoperative myocardial infarction, a number of surgical services have now adopted the policy of having electrocardiograms performed routinely *both* preoperatively and postoperatively on *all* surgical patients over the age of forty

and hyperchloremia following surgery in the region of the hypothalamus and third ventricle

NEUROLOGIC COMPLICATIONS

Cerebrovascular accidents Ischemia of the spinal cord Neurologic complications following spinal anesthesia Puerperal hemiplegia Postpartum pre-eclampsia Precipitation of a myasthenic crisis Considerations relating to the delivery of the pregnant myasthenic patient Hypersensitive carotid sinus Complications of surgery for carotid body tumors The auriculotemporal syndrome Sequelae to the removal of a subdural hematoma Fat embolism Water intoxication

COMPLICATIONS OF RADIATION

COMPLICATIONS FOLLOWING ABDOMINAL SURGERY

Subphrenic abscess Postoperative pneumoperitoneum Complications of counterincision in the diaphragm for the repair of a hiatal hernia Extraperitoneal pelvic abscess Actinomycosis Excessive or unnecessary postoperative procedures following bowel surgery Postoperative pancreatitis Inadvertent gastroileostomy The postcholecystectomy syndromes Other complications of cholecystectomy The postgastrectomy syndromes Acute dilatation of the stomach Problems related to surgery in regional ileitis Bowel impaction Complications resulting from gastrointestinal intubation Extrauterine complications of pregnancy Complications of operative bile duct injuries

INTRODUCTION

ONE of the most important facets of a consultant's diagnostic practice is within the realm of medical surgical problems and obscure postoperative complications Some are iatrogenic, while others are not A number of these entities have already been mentioned under their appropriate sections, but it would be well to briefly set forth a general listing for ready reference when one is faced with these situations The basic philosophy motivating the inclusion of this section was ably summarized by La Due and Wroblewski as follows "An overwhelming curiosity to explain any alteration in symptomatology, temperature, pulse rate, blood pressure, respiratory rate, color, urinary output, or fluid balance will usually lead to prompt recognition of complications that might otherwise result in the death of the (surgical) patient "[16]

The panorama of postoperative sequelae for which medical consultation may be sought is so vast—especially when the various surgical subspecialties are taken into consideration—that only the more important or elusive ones will be discussed here In general, those complications which

ated with most thoracic surgical procedures.[1263j] Furthermore, gravimetric measurement of the blood loss from pneumonectomy usually averages 2000 ml. It may be considerably greater, however, if the procedure requires four or more hours.

Inadvertent and unsuspected trauma to the heart during surgical procedures involving the other thoracic viscera—most notably esophageal surgery and lung resections—probably accounts for a significant incidence *of cardiac arrhythmias and cardiovascular morbidity* (i.e. coronary pain, shock, pericarditis, congestive failure).[1263k]

The use of the serum glutamic oxaloacetic transaminase and related serum enzymatic studies may be very helpful when the diagnosis of myocardial infarction is in doubt (p. 694).[1263l] In this regard, attention is specifically directed to the following situations that might arise: the electrocardiogram taken prior to the evolution of demonstrable changes, the finding of inconclusive ST deviations or T wave changes, the concomitant presence of certain conduction defects, most notably that of left bundle branch block, the identification of acute myocardial injury superimposed upon the remains of old myocardial infarctions with the possible "neutralization" of the induced currents of injury, evaluation of the changes seen on the electrocardiogram following rapid heart action (the post-tachycardia syndrome) (p. 266),[869] and the differentiation of an acute myocardial infarction from pulmonary embolism, pericarditis, digitalis effect and a host of other potential diagnostic considerations.[1263m] The results must be interpreted, however, in light of any associated acute damage to skeletal muscle, liver, brain, or kidney at the time of surgery, and the previous administration of an opiate (p. 274). In coronary operations, the serum transaminase has usually reverted back to normal by the fifth postoperative day in the absence of complications.[1263n]

The decrease in cardiac output, the hypotension, and the hypoxia induced by the Valsalva maneuver consequent to breath holding and cough—either during the induction of anesthesia or in the performance of postoperative tracheal toilet—might result in cardiac arrest or myocardial infarction.[1263o] It has been shown that there is a significant decrease in both the coronary blood flow and myocardial oxygen consumption during the period of hypotension caused by spinal anesthesia.[1263p] Beecher and Todd have implicated the use of the muscle-relaxant anesthetic agents as another possible factor in the cardiac anesthetic death rate.[1263q] With these drugs, myocardial anoxemia might ensue from the diminished venous return to the heart as a result of the lessened diaphragmatic excursions, and from the impaired use of the abdominal and accessory muscles of respiration.

The emphasis upon *surgery for the relief of coronary artery disease* will continue to increase in the future. These procedures pose a number of considerations for the attending cardiologist, many of which were recently summarized by Brofman.[1263r] Operation must not be advised without a sufficiently prolonged period of medical therapy and evaluation (at least six months). This caution is all the more in order when a recent acute myocardial infarction has occurred, or has been suspected. This is especially true in younger patients with progressive symptoms, inasmuch as

five[1263b] As a frame of reference, Etsten and Proger have pointed out that, for all practical purposes, coronary atherosclerosis can be presumed to be present in 50 per cent of individuals in the forty-five to fifty age group, and in most patients beyond the age of sixty years[1263c, d] When the usual precautions are taken in patients with "chronic" coronary artery disease (i e , after being stabilized for at least three months), surprisingly little mortality is attendant upon elective surgery Following a recent myocardial infarction, however, even the more urgent surgery should be delayed for at least three (but preferably six) months, if at all possible

In individuals with known or potential coronary heart disease, considerable emphasis by both the surgeon and the anesthetist must devolve about the avoidance of undue stress (especially during anesthetic induction), hypoxia, undue vasoconstriction, sharp drops in blood pressure (especially with deep thiopental, cyclopropane, and high spinal anesthesia), excessive loss of blood, and factors predisposing both to thrombosis-formation and disturbances in cardiac conduction and rhythm[1263e] With reference to the last, myocardial anoxemia has been precipitated or aggravated by the tachycardia resulting from the use of the anticholinergic agents This is particularly likely when they are administered parenterally[1263e]

Rocco and Vandam have clearly shown that arterial hypotension (with or without bradycardia) resulted from abdominal manipulation in 55 of 68 patients who were carefully studied while continuous brachial artery recordings were being taken[1263f] The average fall in mean pressure was 53 *mm of mercury in 26 patients, with more profound drops being observed* in patients whose physical status was considered poor The hypotension was most pronounced when the manipulations included handling of the liver, movement of the hand in the peritoneal cavity from one area to another, the placement of packing evisceration and retraction of the wound edges This response is apparently one of a reflex nature, resulting from the stimulation of localized receptors (which are probably more abundant in the upper part of the abdomen and in the parietal peritoneum)

Myocardial infarction can also be precipitated by pulmonary embolism, most notably when the latter induces severe shock[1263g] The possibility of a postoperative infarction is ever present in the patient with aortic valvular disease or luetic aortitis (p 258) The high incidence of "painless" myocardial infarction in psychotic patients has been stressed by Marchand This complication should be considered when a previously overactive mentally disturbed patient suddenly becomes docile or quiet in the postoperative period[1263i]

Master and his colleagues have called attention to the important observation that acute hemorrhage from any source (and particularly when within the gastrointestinal tract) may readily lead to coronary insufficiency, along with the associated tachycardia the decrease in blood volume, and the hypotension[1263h] This complication must be anticipated in any patient whose coronary circulation has already been impaired by either cardiac hypertrophy or probable arteriosclerotic disease In this regard, it is estimated that at least 500 ml of whole blood will pass into the pleural space postoperatively as a result of the pleural trauma associ

lytes Progressively severe heart failure following a mitral commissurotomy is apt to result from the presence of concomitant and unaltered aortic valvular disease [856]

Even when early operation is mandatory as in the case of a fractured hip, the urgency is rarely so great as to preclude adequate evaluation of the cardiovascular status of the older patient and full digitalization over a period of several hours, if indicated [1 64a] The ability of the elderly cardiac patient to climb stairs without angina or dyspnea, and to lie flat for prolonged periods without developing a cough or ankle edema are at times much more favorable preoperative criteria for operability risk than the electrocardiogram—or even the physical examination of the individual in question [1264b c] There are many pros and cons to the subject of prophylactic preoperative digitalization in the aged Fortunately, rapidly acting digitalis preparations are readily available should their use become necessary either during or following surgery

There are a number of complications attendant upon the correction of a preductal coarctation These include the precipitation of acute left-ventricular failure if the ductus is ligated initially, and the coexistence of a hypoplastic mitral valve or other valvular anomalies [877c] Similarly, a pulmonic stenosis should always be corrected prior to the ligation of an associated ductus arteriosus in order to obviate the sudden excessive load on the right ventricle and the possible precipitation of acute heart failure This particular combination might be suspected by the presence of sharply peaked P_2 waves and the finding of hypertrophy of the right ventricle in a patient with a patent ductus arteriosus

An arteriovenous fistula may develop following intervertebral disc surgery or a nephrectomy as a result of the inadvertent injury to the vessels lying close by especially the iliacs Such injury has been overlooked even by the best of surgeons Should there be persistent and unexplained tachycardia cardiac enlargement dyspnea and edema of the lower limbs after either of these procedures this possibility must be entertained if the patient is to be spared the subsequent development of a high output circulatory failure [844] The various physical signs suggesting this complication could include unilateral venous dilatation, diminished arterial pulsations, palpable thrills or machinery like murmurs over the lower abdomen and the femoral vessels a widened pulse pressure and increased venous pressure

The Pregnant Patient with Rheumatic Heart Disease The method of management of the pregnant patient afflicted with severe rheumatic heart disease constitutes a problem that frequently confronts the medical consultant Some added pressure has been exerted upon him more recently as a result of the widely publicized successful performance of mitral valvuloplasties in small and highly selected groups of pregnant cardiacs The author at present fully agrees with Dack Burwell, Morgan Jones and others in the following tenets (1) the pregnancy (if normal) should be allowed to pursue its normal course under practically all circumstances (2) such complications as pulmonary congestion anemia and infection must be promptly defined and corrected, (3) heart failure must be treated early and vigorously, (4) all modes of interference with labor must be

their hearts are prone to develop electrical instability and possibly ventricular fibrillation. *It must be emphasized, however, that there is no* absolute correlation between the duration of symptoms and the severity of the underlying process.

The potential harm of superfluous preoperative diagnostic studies in these patients cannot be overemphasized. This is particularly true with reference to gallbladder and gastrointestinal x rays, exercise and anoxemia tests, and intravenous infusions. Such tests are not only exhausting, but frequently increase the patient's apprehension because of the added delay in surgery. Full preoperative digitalization on a routine basis to obviate undesirable tachycardias (digitalis actually *decreases* the operative myocardial irritability), and the avoidance of marked variations in oxygenation (*which might induce dangerous oxygen differentials in the myocardium*)[1263] have enhanced the safety of patients undergoing the Beck and other procedures.

Aortic Stenosis. This condition can be the basis of a myocardial infarction, sudden death, or syncopal episodes associated with surgical stress (p. 258).[859] The murmur is often obscured by congestive failure. Furthermore, in the presence of hypertension, the second aortic heart sound may not be diminished. These patients tolerate postoperative hypotension and overloading of the venous return to the heart by fluids very poorly.

Heart Strain and Failure. Patients with a weakened myocardium are less tolerant of the physiologic sequelae resulting from the possible congestion *and hypoxia attendant upon surgery. These effects can lead to heart* failure, renal and hepatic dysfunction, peripheral thrombosis or embolization, and arrhythmias of various types.[1262]

Surgeons should bear in mind the cyclical edema which many women normally exhibit in timing anticipated operations. In addition to the presence of heart failure, hepatic disease, renal disease and hypoproteinemia, the tendency for emotional stress to exaggerate the cyclical edema which many premenopausal women normally experience should also be recognized. This phenomenon is not only enhanced by the female sex hormones, but also by a secondary hyperaldosteronism which may be initiated and further aggravated by such therapeutic procedures as sodium restriction in the diet and the administration of diuretic agents.[1, 12b]

It is recalled that extensive cardiac involvement may occur not only in the primary form of amyloidosis—whether systemic or localized to the heart[8, 9b]—but also in the amyloidosis secondary to long standing tuberculosis and pulmonary suppuration.[198, 0] The syndrome of idiopathic myocardial failure in the last trimester of pregnancy and in the puerperium should be *considered in the patient who develops unexplained heart failure* during these periods, especially when the stigmata of rheumatic or hypertensive heart disease are absent.[84b]

It may be difficult to diagnose early heart failure after a pulmonary resection (particularly a pneumonectomy) because of the congestion and basilar rales that usually follow the temporary increase of blood flow in the remaining lung. The overloading of the circulation *in certain patients* undergoing pneumonectomy can be very hazardous and might lead to pulmonary edema, whether the infusions consist primarily of blood or electro-

traindicated because of the hazards attendant upon myocardial depression On the other hand one must carefully attempt to ascertain a history of previous cardiac standstill or rapid ectopic rhythms in view of the great value of prophylactic atropine and antifibrillary therapy, respectively, in such instances Furthermore, quinidine or Pronestyl may be of considerable help in the management of patients with cardiac syncope due to ventricular arrhythmias that are *not* associated with heart block

Auricular fibrillation occurs relatively frequently in patients with basically normal rhythms the first week following a commissurotomy, there is usually little danger, however if the patient has been routinely digitalized In one series of 77 patients who had a normal sinus rhythm prior to the performance of a mitral valvuloplasty atrial fibrillation developed in 47 per cent—most frequently on the second postoperative day [1624k] In view of the spontaneous resumption of a sinus rhythm in many of these individuals quinidine may be withheld for as long as one week if no urgency exists and the patient is adequately digitalized Reversion of a chronic auricular fibrillation to normal rhythm after a successful valvuloplasty and in the absence of clots in the left atrium should be seriously considered It is well known that uncontrolled auricular fibrillation *per se* can result in congestive failure, even in individuals with basically normal hearts [834] A marked increase in both the cardiac output and exercise tolerance has been recorded in many patients who were so converted [1 641]

While auricular fibrillation or flutter is commonly noted shortly after thoracic or cardiac surgery its late onset (i e, more than ten days postoperatively) suggests serious postoperative complications or reactivation of an underlying rheumatic process Auricular fibrillation is apt to be a particularly poor omen when it develops after surgery for carcinoma of the esophagus [1 641] As a rule, auricular fibrillation occurs infrequently following surgery for congenital cardiac lesions [1 64k]

Cardiac Arrest during and after Surgery When it occurs in the operating room this catastrophe is due to ventricular standstill nine times out of ten It is very important to be cognizant of the several groups of patients who are particularly vulnerable to this complication, inasmuch as electrocardiographic monitoring and an already attached pacemaker should be seriously considered in these instances Such situations include the following extreme debility, severe coronary cyanotic or valvular heart disease congestive failure, the presence of A-V block of *any* degree patients receiving large doses of either quinidine or Pronestyl the very young or old hyperkalemia and previous episodes of cardiac arrest [1263 1265] In regard to the last it is also stressed that once a patient has been resuscitated during surgery constant monitoring with a monitor pacemaker device is mandatory for *at least* two more days, since a number of these individuals have succumbed to a subsequent episode of postoperative cardiac arrest

The possibilities of myocardial infarction pulmonary embolization, and cardiac trauma must also be entertained when standstill occurs postoperatively Cardiac arrest might follow fibrillation (countershock) for ventricular fibrillation in which case the artificial pacemaker or manual systole is necessary [1265e] The use of cortisone should be considered in patients with

shunned *unless* there are legitimate obstetric difficulties and indications, and (5) a cesarian section should be done *only* for obstetric indications and then only after every effort has been made to achieve the maximal cardiac improvement possible[838]

Disorders of Rate and Rhythm Overdigitalization (p 244), increases in the volume of extracellular fluid, and the effects of hyponatremia and hypokalemia tend to be perpetuated or exaggerated in the cardiac patient by the ordinary endocrine and metabolic responses to surgery These conditions occasionally account for some of the conduction defects and ventricular tachycardias encountered during anesthesia even when the classic signs of toxicity are absent[1264d] Black and Harken have emphasized the frequency with which overdigitalization resulting in cardiac irritability has been a problem in patients coming to valvular surgery[1264e]

Disorders of rate and rhythm may also be induced by improper pulmonary ventilation, the position of the patient, hypotension, inadequate digitalization, respiratory acidosis (carbon dioxide retention), and the excessive use of atropine or meperidine (Demerol)[1264f] During epicardial abrasion in coronary operations, bouts of ventricular premature beats and ventricular tachycardia frequently occur, but are almost always transient[1263a] Even when the transaortic approach is employed for the correction of aortic stenosis, there remains an appreciable risk of ventricular fibrillation[859c]

Rapid ectopic rhythms in the postoperative period are more serious in the older age groups, auricular fibrillation being the one most frequently encountered They often lead to congestive failure, myocardial infarction, or sudden death[1264g] Operation should be postponed in the patient presenting himself in the operating room with an unexplained tachycardia[1 54a] In this circumstance, previously unsuspected organic heart disease or a low blood volume—rather than a presumed diagnosis of apprehension—must be seriously considered Anesthetists are aware of the fact that *while* the pulse rate is often misleading the quality of the pul e is usually a sign of considerable value

Arrhythmias are very prone to occur after thoracic operations, particularly pulmonary resections on the right side[1264m] It has been suggested that the involvement of the vagal nerve fibers by mediastinal invasion secondary to a carcinoma of the lung or esophagus predisposes patients to arrhythmia formation Other vagal reflexes may be initiated by mediastinal shifts, pleural fluid, tracheal intubation or aspiration, a stitch abscess or a tight chest binder

The author has been impressed by the frequency with which cardiac arrhythmias and arrest occur during the course of cataract surgery Others have stressed the frequency with which these abnormalities take place in youth during strabismus operations Such complications presumably occur because of the high vagal tone during adolescence and the greater activity of the oculocardiac reflex while the patient is under anesthesia[1265b]

In general, preoperative medication with atropine that is given in an attempt to prevent uncontrollable arrhythmias should be *avoided in patients undergoing mitral valve surgery* Similarly, the routine prophylactic use of either quinidine or procainamide hydrochloride (Pronestyl) is con

sitating pericardial manipulation and inflammation develop electrocardiographic changes attributable to pericarditis These changes might be read ily mistaken for those of acute myocardial infarction Such instances of surgical pericarditis are prone to have an early onset (even within hours) and to take a rapid course Cahué and Pick have observed that it is not uncommon to see a rapid regression of the acute alteration with a restitution to the preoperative pattern within one or two weeks [L-641] In these cases, the usual immediate patterns of pericarditis (i e , flattening and inversion of the T waves) may not appear Smith and his colleagues have encountered an extraordinary incidence of acute benign pericarditis in children with Cooley s anemia who were subjected to splenectomy [5]

Profound degrees of ST segment depression and elevation in the unipolar leads are particularly apt to occur following epicardial abrasion These changes may be long standing or even permanent [L-63n] Inasmuch as most patients who undergo mitral surgery are digitalized, it is important to appreciate the fact that the particular configuration of the final deflection represents the resultant of the pericarditis (which tends to elevate the ST segment) and the digitalis (which tends to depress and to shorten its duration) The majority of cases of surgical pericarditis following mitral commissurotomy are either preceded or accompanied by auricular fibrillation or flutter

Hemopericardium and Pericardial Tamponade The frequency with which pericardial tamponade is missed in its acute phases and the great value of a pleuropericardial "window' in decompressing the pericardium were discussed at length in Group IX (p 254) In one series of 17 cases, dyspnea was encountered universally [849] In fact this sign was frequently misconstrued as representing primarily congestive failure or pulmonary disease The diagnostic importance of pulsating neck veins when the patient is in the upright position and an exaggerated "pulsus paradoxicus (which is most accurately determined with the sphygmomanometer) along with a number of misconceptions which still preclude the early diagnosis of acute tamponade, were also stressed previously

Undiagnosed and fatal hemopericardium has been reported subsequent to unrecognized trauma to the heart during surgery on the lungs and the esophagus [1 6 k] It is not generally appreciated that there is ample clinical and experimental evidence to indicate a definite etiologic relationship between hemopericardium resulting from various causes and the subsequent development of a constrictive pericarditis [850] Complete evacuation of the hemopericardium either by repeated pericardicenteses or pericardiotomy, should be attempted in order to avert this complication

Failure of Surgery for Constrictive Pericarditis As a result of the studies by Burwell and others, it has become clear in recent years that the major objective in this type of surgery is the decortication and release of the two ventricles rather than relieving the effects of the scars surrounding the atria and the great veins (p 255) [851] The presence of diffuse myocardial fibrosis may not only mimic all the manifestations of constrictive pericarditis but can complicate the latter disorder If this complication exists, even the most skillful resection will be of no avail

An associated constrictive pleuritis due to fibrosis of the pleura was a

myocardial infarction who develop Stokes Adams attacks, since striking improvement has occasionally been observed following such therapy [1 651] The benefit presumably is due to the reduction in the postinfarctional inflammation that affects the conduction tissues in the septum, and also possibly to a direct accelerating effect on atrioventricular conduction

To prevent standstill in the operating room, it is important to avoid excessive anesthetics (the dose of ether being limited to 30 cc for a procedure lasting one and one-half hours), hazardous combinations (particularly cyclopropane and epinephrine), hypoxemia (by insuring a clear airway, sufficient oxygen, adequate hemoglobin and circulating blood volume, and an adequate pulmonary exchange), and hypercapnia With atropine, one can also depress the excessive vagal reflex activity that is apt to occur during intubation, extubation, inadvertent tracheal stimulation during thyroidectomy, inflation of the urinary bladder, and manipulation of either the pulmonary hilus, the mesentery, or the carotid sinus areas [1265c] The atropine should be given at least every four hours *by the clock*, especially *during prolonged operations*

Notwithstanding the great risk involved in surgical intervention with *any* anesthetic agent, emergency surgery can often be successfully carried out in patients with heart block—even those with previous Adams Stokes attacks The many prophylactic and therapeutic considerations involved in the safe conduct of these patients through operations have been reviewed by Vandam and McLemore [1 65g] The value of a continuous intravenous infusion of isopropylarterenol (Isuprel), prevention of respiratory acidosis, use of molar sodium lactate, and monitoring devices is emphasized

One needs to be alerted to the fact that reflex circulatory arrest is occasionally encountered in young and apparently healthy individuals with no overt heart disease during a number of diagnostic procedures The latter include jugular puncture, intravenous pyelography, bronchography, *cardiac catheterization, and endotracheal intubation* [1265d]

Considering the drastic measures that must be immediately taken when it occurs (viz, within a period not exceeding several minutes), the importance of a correct diagnosis of cardiac standstill is at once apparent It can usually be made by the observant anesthetist upon his noting absence of the carotid pulse, the heart sounds, the respriations, and the blood pressure and by the wide dilatation and fixation of the pupils It must be emphasized that if one can hear heart sounds—even in the absence of major arterial or peripheral pulsations—standstill is *not* present (Operating rooms should be equipped *at all times with an extra stethoscope specifically* intended for emergency cardiac auscultation) Since there is a disappearance of the retinal arteries along with segmentation of the venous blood in the retina within seconds after the circulation stops ophthalmoscopic examination might offer anesthetists, internists, and surgeons alike a rapid and objective means for determining cardiac arrest [1 65f] The venous segments may continue to move for several minutes, however during which time cardiac resuscitation could be successful

Hypothermia has been used with success in reversing the brain damage due to cardiac arrest

Postoperative Pericarditis A high percentage of patients who have been subjected to pericardiotomy or to other types of chest surgery neces-

able breaks in sterile technique (p 118)[418, 419, 1641] This is particularly important in the case of a staphylococcic endocarditis occurring within one week to three months after a mitral valvulotomy This complication may become manifest primarily as unexplained fever and malaise In seven such cases none of the classic signs of endocarditis (petechiae, splenomegaly, clubbing of the fingers) could be found In fact, five were treated with anticoagulants because of a presumed diagnosis of pulmonary infarction[419]

In one large surgical cardiac clinic postoperative endocarditis occurred once among 374 patients with congenital heart disease who were operated upon, and in 19 instances among 1889 patients with acquired valvular heart disease[418b] The high incidence of infection with the *Staphylococcus* (14 cases) aortic valvular disease and heavy valvular calcification was striking In spite of intensive antibacterial therapy, death ensued in 12 of these patients The malignant nature of the infection was attributed to the trauma imposed upon the valve the invasion by antibiotic resistant organisms, and the severe stress to which these patients were subjected

Recent observations have tended to implicate the occurrence of staphylococcal abscesses in the heart or great vessels following surgery to the use of silk suture material[419c] (It has been long recognized that silk sutures can exert an important influence upon both the localization and the persistence of infection in other areas of the body) Following this lead, abscesses at these sites that proved to be resistant to large doses of antibiotics were finally successfully treated by the removal of the silk sutures from the infected area

Undiagnosed Multivalvular Disease Other complications of mitral valvuloplasty are apt to ensue in the presence of undiagnosed multivalvular disease, particularly with reference to aortic stenosis and tricuspid stenosis[856, 857, 865] The reader is referred to a comprehensive discussion of this entire subject in Group IX in which the postoperative complications stemming from unrecognized valvular abnormalities were stressed (pp 260–264) For example if a tricuspid procedure is not performed immediately after operation on a stenosed mitral valve manifestations of tricuspid stenosis will often be precipitously increased[865a] Not only are patients with significant degrees of mitral insufficiency not benefited by the presently available procedures but it is known that these patients commonly manifest considerable intolerance to anesthesia

Recurrent Mitral Stenosis The problem of "recurrence" of mitral stenosis following previous surgery upon this valve has been deliberated at considerable length by cardiologists and cardiac surgeons Many regard the re-establishment of such an obstruction as basically due to either failure to relieve an associated subvalvular obstruction or to the incomplete splitting of the fused commissures at the time of the initial procedure The latter technical difficulty has often stemmed from the widening of but a single commissure and from reliance solely upon digital pressure In approximately 20 per cent of his first 1200 mitral operations, Bailey encountered a significant degree of subvalvular obstruction to the blood flow that was created by a complex interfusion or cross fusion of the chordopapillary supporting tissues[865b] Mechanical separation of such subvalvular adhesions is often necessary for a satisfactory result

significant factor in the postoperative disability of 50 per cent of Burwell's patients Moreover, in some instances, this pleural pathologic condition appeared to be definitely *aggravated by the surgery The presence of long* standing congestive changes in the liver, the development of hypertension, and the activation of the tuberculous process might all contribute to an unfavorable postoperative course[851b]

Other Causes of Electrocardiographic Abnormalities In addition to myocardial infarction, pericarditis, and pulmonary embolism, marked ST segment and T wave changes can be induced by potassium deficiency, other electrolyte imbalances, the post tachycardia syndrome, prolonged hypotension, hypercapnia, hypoxia, and certain drugs In the case of post tachycardia syndrome (p 266)[869c] and certain electrolyte imbalances (particularly hypokalemia), the associated T wave changes may closely simulate those of a myocardial infarction of the subendocardial type

When compared with the preoperative tracings, postoperative changes in the electrocardiogram were noted in 50 per cent of one series of patients who were subjected to resectional surgery or to thoracoplasty[1264h] The authors believed that many of these differences could be most readily explained by the induced positional changes of the heart and the mediastinum Similarly, the importance of the time factor in postoperative electrocardiography must be emphasized There is a shift of the mediastinum to the unoperated side immediately following most types of thoracic surgery, later, the shift occurs toward the operated side These changes result not only in a shift of the so-called transitional zone, but also in T wave inversion in leads V_2 and V_3 The latter findings might lead to an erroneous diagnosis of pericarditis, coronary insufficiency, or pulmonary heart disease with right ventricular hypertrophy if reference is not specifically made to the cardiac position

The Postcardiotomy Syndrome This complication is observed in approximately one out of every three patients with rheumatic heart disease who are subjected to a cardiotomy, with or without a valvuloplasty It is characterized by fever, pleuropericardial chest pain, and occasionally congestive heart failure, pleural effusion polyarthritis, various arrhythmias, abdominal pain, and subcutaneous nodules Steroid therapy has been demonstrated to be effective as both a prophylactic and therapeutic measure[1264l 1266]

Attention is directed to the importance of a careful study of the rectal temperature readings over a period of several days for evidence of rheumatic activity in every patient being considered for rheumatic valvular surgery Epstein has recently reviewed the various evidences for and against the theory that the postcommissurotomy syndrome is of rheumatic origin[1266b] Larson has pointed out that a disorder indistinguishable from the postcommissurotomy syndrome is occasionally observed following chest surgery that is performed for a variety of congenital or acquired diseases which bear no relationship to rheumatic fever[1266c d]

Postoperative Endocarditis It behooves all surgeons and cardiologists to anticipate the possibility of an endocarditis following mitral or aortic valve surgery, ligation of a patent ductus and other types of cardiac surgery with vigorous combined *antibiotic therapy because of the* unavoid

Prior to the actual open heart surgery the ability of the patient to tolerate extracorporeal perfusion can be studied by its effect on electroencephalographic tracings (taken with small portable machines in the operating room)[1267f] Many of the "kinks" relating to the safety of pump-oxygenators have already been solved, with particular reference to the avoidance of gram negative sepsis by the introduction of inexpensive plastic units that can be thrown away after one perfusion Some centers have encountered difficulty with the metabolic acidosis induced by these by pass mechanisms in which there is a proportionately larger rise in the blood lactic acid than in the carbon dioxide levels

With the availability of these better operative procedures, however, other vexing problems will be encountered by the clinician These might be anticipated to some extent by careful preoperative evaluation One example of this therapeutic paradox can be found in the case of interventricular septal defects that are corrected, but following which acute right-heart failure ensues in short order The latter apparently results from the associated severe pulmonary arteriolar sclerosis that has developed in response to the long standing severe pulmonary hypertension Consequently the lungs are not able to handle the total circulation now being diverted to them because of their occluded arterioles[8790] The postoperative prognosis tends to be especially poor when the pulmonary arterial pressure approaches or surpasses 80 per cent of that of the systemic blood pressure

Surgical and Anesthetic Problems Unique to Negroes It is not generally realized that the American Negro's physical and psychological reactions to anesthesia surgery and even to obstetrics still incur a mortality rate of from two and one half to four times greater than that encountered in comparable groups of white patients[1 74] Essential hypertension cardiovascular crises eclamptogenic toxemia with convulsions, and racial melancholia characterize these aberrant responses to stress situations

An excessive sympathetic nervous system storm due to the discharge of considerable epinephrine and norepinephrine which might underlie this increased mortality has been inferred from observations such as the following labile hypertension is noted in 70 per cent of surgical colored patients on admission sharp changes in the blood pressure commonly occur during surgery while the patient is under general anesthesia the frequent difficulties encountered in stabilizing the blood pressure when hypotensive techniques are employed marked contractions of the veins of the skin are often observed before intravenous injections and after the introduction of needles (at times resulting in undue delay in starting emergency transfusions) and the occurrence of marked changes in the blood glucose levels during surgery The problem is further complicated by the pigmentation of the Negro which may camouflage anemia during the physical examination, and cyanosis during anesthesia surgery, childbirth and infant resuscitation

There is both a high maternal mortality rate and considerable fetal wastage associated with pregnancy in individuals afflicted with the sickle cell disease and probably some of its variants[713]

While recurrence of mitral stenosis will undoubtedly become less frequent with the availability of more adequate means by which both mitral commissures can be mobilized (such as the performance of the commissurotomy from the right side), the tendency to stenosing will inevitably continue in these individuals once the basic valvular pathologic condition has become sufficiently established. For example, Bailey and his group have reported on 22 patients with recurrent symptoms following a mitral commissurotomy that were attributable to restenosis, on 16 of whom operation could be performed again.[857c] Craige has recommended the phonocardiogram as a readily performed objective criterion for both the severity of mitral stenosis and the actual improvement that is produced by surgical procedures on the mitral valve.[857d] He found that the most reliable guide—provided the heart rate was not too slow—was the index derived from the delay of the first heart sound (with respect to the onset of the QRS complex) and the interval between the second sound and the opening snap (Q 1-2-OS). This measure also appears to correlate well with the valve's size.

Problems Attendant upon Open Cardiac Surgery and the Use of Extracorporeal Perfusion. There can be little doubt that these techniques (which have been developed in recent years through the genius and courage of Lillehei and others) will continue to be improved upon as they assume an ever increasing place in the definitive correction of congenital and acquired cardiovascular defects. As a result, we have already witnessed the cure of such disorders as interventricular septal defects, the tetralogy of Fallot, intracardiac myxomas, and even rupture of one of the sinuses of Valsalva in significant numbers of patients—feats which were virtually impossible but five years ago.[1 67b c e] Even such pathologic conditions as pulmonic stenosis and acquired aortic stenosis, for which satisfactory operations were previously available, will undoubtedly receive better anatomical correction by direct open heart surgery.[1 87e]

Only several of the problems encountered will be related here. There is no coronary circulation during the cardiac asystole that is induced with potassium chloride or other agents. While this situation is usually tolerated relatively well, the risk of myocardial anoxemia becomes considerable in the presence of marked left ventricular hypertrophy, as in the case of aortic stenosis. In such instances, retrograde coronary perfusion is in order. Kolff and his associates have ably summarized both the advantages and the disadvantages of elective cardiac arrest with potassium citrate during open heart operations as follows: *Advantages*—a motionless field, a relatively bloodless field, less operative blood loss, and greater ease of approximating margins or even large defects in the flaccid heart without prosthesis. *Disadvantages*—the dryness of the operative field might increase the likelihood of coronary air embolism, the prolonged hypoxia might induce myocardial necrosis, inability to recognize interference with conduction in the still heart, inability to recognize the creation of *excessive distortion* in the flaccid heart when large defects are closed, and the production of tears after the restoration of the heartbeat due to unrecognized tension that may be created in the flaccid heart.[1267c]

in the left side-down position when cessation of respiration, shock and an audible "mill wheel" murmur over the precordium are encountered

It is now generally agreed that oxygen via the presacral route in retroperitoneal pneumography is no safer than air, and that carbon dioxide is apparently the only really safe gas to use in this procedure [1 96] The safety of *pure* carbon dioxide is demonstrated by the following two recent uses of this gas (which is 20 times as soluble in serum as is air or oxygen) (1) the flooding of the entire thoracic cavity and the opened portions of the cardiovascular structures with gaseous carbon dioxide during heart lung by pass procedures in an attempt to reduce the risk of gaseous embolization,[8590] and (2) the intravenous injection of pure carbon dioxide as a means of contrast roentgen visualization of the intravascular structures *

Nicholson has reviewed this problem comprehensively and has set forth the following useful etiological classification of air embolism [1 97]

Surgical

1 Operations involving the veins of the neck thorax or pelvis
2 Operations of the direct vision type on the heart
3 Operations resulting in the opening of the dural sinuses or the veins around the cervical and upper thoracic vertebral column performed with the patient in the sitting position
4 Uterine curettage followed by air insufflation

Diagnostic air injections

1 Into the peritoneal cavity
   a direct
   b indirect (the Rubin test)
2 Into the presacral cavity urinary bladder and large joints
3 Encephalography and angiocardiography

Therapeutic air injections

1 Maxillary antrum lavage
2 Pneumoperitoneum and pneumothorax
3 Vaginal powder insufflation especially during pregnancy

Obstetrical

1 During delivery when patient has a placenta praevia
2 Attempted criminal abortions

Accidental entrance of air

1 Through faulty intravenous apparatus
2 Following the use of air pressure to speed up transfusion therapy

Complications of Induced Hypothermia This technique by reducing both the oxygen consumption and metabolic needs of the hypothermic tissues has found increasing use in intracardiac surgery, neurosurgery, the resection of thoracic and aortic aneurysms, and as an adjunct to conventional surgery It has been demonstrated that moderate hypothermia protects the brain against the effects of sudden hypoxia by reducing the cerebral metabolic rate It also tends to reduce the adrenal mediated stress reactions that accompany surgery For example patients subjected to this

* See reference 242 of Part II

VASCULAR COMPLICATIONS

Phlebothrombosis, with or without Embolism or Phlebitis By virtue of their frequency and possible prevention, these conditions must receive prime consideration in *every* surgical or postpartum patient who exhibits sudden chest complications (p 212)[769, 771] Amniotic fluid embolism has also resulted in serious postpartum sequelae[456] The sudden cessation of dicoumarin in individuals who have been on long term anticoagulant therapy may induce a state of rebound hypercoagulability, leading to subsequent coronary or peripheral vascular thrombosis[1267a] Intravascular thrombosis infrequently results from the rebound thrombocytosis that follows a splenectomy, but is more prone to do so in the presence of myeloid metaplasia (p 203) Significant obesity should be regarded as one of the chief hazards in the elderly patient undergoing major surgery, primarily because of the frequency of thromboembolism[1048b]

Fat Embolism This complication is likely to follow fractures, extensive soft tissue injuries, and either the excision of or trauma to large amounts of fat at the time of surgery Fever, tachypnea, neuropsychiatric changes, and petechial hemorrhages make their appearance following a latent period of several hours to days (p 216)[79, 794] Peltier has shown that it is possible to cause sequestration of the released fat in an extremity during an operation upon bone by the use of a tourniquet[794b] This maneuver apparently prevents the fat droplets from reaching the systemic circulation When the possibility of fat embolism is raised clinically, Love and Stryker have suggested the use of both intravenous 5 per cent glucose 5 per cent alcohol infusions for the emulsifying effect of this particular combination, and of heparin for its activating effect on the lipoprotein lipase[794a]

Atheromatous Emboli to the Kidneys after Aortic Surgery The magnitude of this particular complication following corrective surgery that is performed for either aneurysms of the abdominal aorta or for an atherosclerotic occlusion of this major vessel is receiving greater attention by both surgeons and pathologists Acute emboli of atheromatous material were found in 17 of 22 patients who died after this type of surgery at the Massachusetts General Hospital[911] Several of these individuals exhibited a strikingly similar clinical picture They appeared to tolerate the elective procedure well with no evidence of shock In the postoperative period, however, anuria or severe oliguria asserted itself and was followed in turn by a progressively fatal uremia

The primary pathologic changes found at postmortem examination consisted of multiple renal infarcts that were caused by these atheromatous emboli It would appear that the pathogenesis of this complication rests in the fragmentation of the atheromatous plaques from the wall of the aorta that occurs just proximal to the site of its clamping and manipulation This area is also simultaneously the site of considerable turbulence

Air Embolism The number of diagnostic, therapeutic, and surgical procedures that can predispose to air embolism is continually increasing This complication must be considered and the patient immediately placed

Attention is called to the very high incidence of "premonitory" apprehension anxiety, and related mental symptoms preceding a major pulmonary embolus.[777a] The electrocardiographic changes can be manifold, ranging from the classic patterns of acute cor pulmonale and coronary insufficiency to changes in the electrical position of the heart or very minor and transient phenomena. The reader is referred to the more detailed discussion of pulmonary embolism in a previous chapter (p. 212).

Pneumonitis, with or without Atelectasis. These important complications are ever present and must be considered when postoperative fever occurs in heavy smokers, in patients with pulmonary congestion following extensive upper abdominal or thoracic procedures, in elderly individuals with poor cough reflexes, following the wearing of tight binders, and with the use of excessive amounts of atropine. Insufficient attention has been directed to the extraordinary degree of bronchorrhea and subsequent atelectasis that is prone to develop in patients with a mild "wet" bronchitis during and after operation, irrespective of the type of anesthesia employed. Emphasis upon the degree of "wetness" of the preanesthetic-induced cough has proved of great value in anticipating and preventing these sequelae.[1270a] Furthermore, considerable bronchospasm and laryngospasm are apt to be encountered by anesthetists during the induction of anesthesia in patients who did not refrain from smoking for at least one week prior to elective surgery.

In patients with bronchial asthma, postoperative atelectasis may be massive.[1270b] The occurrence of x-ray shadows resembling a V-shape or a "cluster of grapes" (particularly in the upper lobes), fever, hemoptysis, and chest pain in the patient with asthma or obstructive bronchitis suggests mucoid impaction of the bronchi (p. 128).[449]

When faced with the problem of copious tenacious postoperative tracheobronchial secretions, a prophylactic tracheotomy to prevent hypoxia, atelectasis, and pneumonitis frequently carries the least risk. It has become a dictum that the best time to perform a tracheotomy for proper tracheobronchial toilet is usually when one is contemplating the procedure. The need for an "optimal" rather than an "adequate" airway must be continually stressed.

The induction of hyperventilation postoperatively for the prevention of atelectasis can be achieved in a very simple manner by adding 1000 cc. of dead space in the form of a long rubber tube through which the patient rebreathes for five minutes every two hours.[1270c] Most patients will readily tolerate the decrease in $_pCO_2$ that takes place after two minutes. Any hypoxia may be obviated, if necessary, by directing a flow of oxygen (about 3 to 4 liters per minute) into the distal end of the tube.

The re-expansion of the lung segments that have been collapsed for long periods during extended operations has occasionally resulted in pulmonary edema. The clinician should always bear in mind that pulmonary edema predisposes to pneumonitis, and vice versa (p. 129).[453] There is a significant incidence of expansion problems in patients subjected to segmental resections, either alone or with wedges. Reference is briefly made again to the high mortality that is currently being encountered in cases of

procedure fail to demonstrate the anticipated retention of water and salt during the early postoperative period[1268a]

The major and most feared complications of hypothermia are ventricular fibrillation and cardiac standstill[1268] The infusion of trimethapan camphorsulfonate (Arfonad) appears to prevent myocardial irritability during cooling and can eliminate arrhythmias resulting from the myocardial irritability to a large degree[1268a] Since the ventricular irritability also appears to be related to excessive citrate levels and the attendant reduction in the ionized serum calcium levels, heparinized blood transfusions during hypothermia are probably to be preferred

Other sequelae include peripheral neuropathies,[1137b] coronary air emboli, hemorrhage after rewarming (largely due to the platelet loss), metabolic acidosis and cardiac dilatation with shock (resulting from the too rapid return of the blood flow to the heart after occlusion) Hypothermia might prove to be disastrous in the presence of severe occlusive vascular disease

Complications of Induced Hypotension This technique of instituting a "physiologic trespass" by various means is employed primarily to diminish the amount of capillary bleeding in the operative field Consequently, it has found its greatest usefulness in the surgical treatment of vascular malformations and tumors of the brain and in extensive block resections for cancer Complications (both fatal and nonfatal) are directly related to the duration and degree of hypotension the critical level being 80 mm of mercury

In an analysis of 28,000 cases subjected to this procedure, complications were noted in one out of every 31 patients[1 69a] These included reactionary hemorrhage (bleeding from the operative site upon restoration of normal blood pressure), delayed awakening blurred vision postoperatively persistent hypotension, anuria or oliguria, cardiovascular collapse, cerebral thrombosis, cardiac arrest, coronary thrombosis, and retinal thrombosis It is also pointed out that an unusually high incidence of fatal acute peptic ulceration is currently being encountered following cardiac surgery This complication is particularly prone to occur with the combination of prolonged hypotension and a past history of ulcer[1269b]

PULMONARY, PLEURAL AND PULMONOCARDIAC COMPLICATIONS

Pulmonary Embolism This complication must always be seriously considered when angina pectoris, myocardial infarction, unexplained rapid heart action, and syncopal or anxiety attacks occur postoperatively—even in the absence of cough, pleurisy or hemoptysis[769, 776, 778] While pulmonary embolism most often makes its clinical appearance from the eighth to the fourteenth day postoperatively, it manifests itself during the first week in one out of four such cases, and in a similar percentage of these patients after the second week[776b] Furthermore, it should be anticipated following extended pelvic abdominal procedures prolonged hypotension, and in the presence of heart disease, obesity dehydration and the sudden cessation of anticoagulant therapy[1267a] Embolism from the iliac or pelvic veins might ensue, notwithstanding a previous femoral vein ligation

a careful preoperative evaluation of pulmonary function, especially when the vital capacity is found to be below 50 per cent of the predicted normal

Ventilatory function can be determined more accurately by the timed vital capacity, the maximum breathing capacity, the residual air volume the "ventilatory reserve," and bronchospirometric examination (See Section IX of Part II, pp 785–787) The patient must be regarded as a very poor risk if the MBC is 30 L/min or less, if the residual air exceeds 50 per cent or if the "ventilatory reserve" is 80 per cent or less [12 a-c] When evaluating operative risk in the presence of a chronic "wet" bronchitis or marked bronchospasm, it is important that these tests of total pulmonary function be performed only after antibiotics bronchodilators positive-pressure breathing, adequate rest, and postural drainage have been instituted

The standard thoracoplasty, as originally devised for adequate collapse of upper lung tuberculosis, incurs an excessive loss of pulmonary function due to the attendant collapse of much good lung tissue, the trauma to the muscles and nerves of the chest wall and the shoulder girdle and the frequently resulting scoliosis Considerable vital lung function can be preserved by resection with or without a concomitant or subsequent "tailoring" thoracoplasty This is particularly true in the case of multiple bilateral segmental and local excisions for extensive localized tuberculous foci [127 c] When bilateral resections are to be performed experience has shown the advantage of operating upon the more involved side first [1 7 d]

Although the posterolateral approach affords the best exposure for pulmonary resection, it is poorly tolerated by some patients inasmuch as it impairs the ventilatory exchange during the operative procedure Intentional or inadvertent ligation of the phrenic nerve during thoracic operations also can contribute significantly to the degree of ensuing pulmonary insufficiency The use of phrenic nerve interruption should be employed with great discrimination since there are a greater number of postoperative complications following any subsequent surgery and since return of function might never occur Phrenemphraxis has been of limited use in patients with persistent "air leaks" following pulmonary resections [1 7 d]

While more complex in execution and not actually necessary in the evaluation of most patients being considered for surgery pulmonary function studies dealing with the interchange of gases—both of a distribution and diffusion nature—can be helpful in certain instances (i e pulmonary fibrosis emphysema bronchial obstructions emphysematous blebs) (p 787) [1 72 b] Occlusion of the pulmonary artery to an adjacent lobe after resectional surgery (occurring either spontaneously or as a result of injury or ligation) might be followed by profound impairment of pulmonary function This can be very subtle, however being manifested as a marked decrease in oxygen uptake by the affected lung, even though the maximum breathing capacity has decreased but slightly The extent of both the fibrosing process and the concomitant impairment of blood supply in extensive tuberculosis as they affect lung function are also shown by the little improvement in gaseous exchange that takes place in re-expanded lungs following decortication [127c]

The pulmonary hypertension that frequently occurs in the older pa

postoperative staphylococcal pneumonia caused by antibiotic resistant organisms (p 121)[549, 550]

One of the more frequent preoperative and postoperative complications of corrective surgery performed on infants with serious congenital heart disease, particularly when characterized by increased pulmonary blood flow and pulmonary hypertension, is that of massive atelectasis of the left lung In all probability this results from the compression of the left main bronchus by the left pulmonary artery[1270d]

Aspiration as a Complication In one study of 300 patients who underwent general anesthesia, 26 3 per cent regurgitated gastric secretions It is also of considerable importance to note that 16 3 per cent aspirated their gastric contents even with an intratracheal tube in place[1271a] In another series of 926 patients who were prepared for surgery, Berson and Adriani found that 14 per cent regurgitated gastric contents into the pharynx, and that 7 per cent had aspirated these contents into the trachea and bronchi[1271b]

Every experienced surgeon and anesthetist can vouch for the considerable morbidity and high mortality accompanying an aspiration pneumonitis Particular emphasis is directed to the fact that when marked intestinal obstruction and distention or massive upper gastrointestinal bleeding are present, one should not expect to obtain complete gastric drainage either from an in lying Miller Abbott tube or a Levin tube

One cannot use the physiologic emptying time of the stomach as a guide for assuming that the stomach is empty In fact, fatal aspiration of the gastric contents fifteen hours following the last known meal has been reported[1271c] Several anesthesiologists are now using a double-lumen gastric tube with an inflatable cuff which is distended in the lower end of the esophagus during surgery and general anesthesia This is of particular value if emergency surgery is required when the stomach is full, and when the use of spinal anesthesia is contraindicated because of peripheral circulatory collapse in patients with intestinal obstruction and gastric distention[1271c]

The possibility of an aspiration pneumonitis must be entertained and immediate bronchoscopy instituted, along with intensive antibiotic therapy, when unexplained fever and tachycardia occur postpartum in a patient who has had convulsions Fatalities continue to occur from this complication in the puerperium simply because it is not recognized[1271d]

There is a definite risk of tracheobronchial aspiration of vomitus following topical anesthesia of the pharynx, a consideration that must be constantly borne in mind when the patient is unconscious When large quantities of sputum are present it has been found desirable to delay operation until the late morning or early afternoon This will allow time for the elimination of the accumulated overnight secretions[1631] Overholt has emphasized that where it is feasible in performing chest surgery, the posterior approach with the patient in the face down position considerably reduces the danger of spilling secretions into the contralateral lung field

Respiratory Insufficiency The increasing emphasis upon salvage surgical procedures in poor risk patients with extensive emphysema, pulmonary fibrosis, or advanced tuberculosis has asserted itself in recent years In these patients, pulmonary failure must be anticipated and prevented by

a careful preoperative evaluation of pulmonary function especially when the vital capacity is found to be below 50 per cent of the predicted normal

Ventilatory function can be determined more accurately by the timed vital capacity, the maximum breathing capacity, the residual air volume, the "ventilatory reserve" and bronchospirometric examination (See Section IX of Part II, pp 785–787) The patient must be regarded as a very poor risk if the MBC is 30 L/min or less, if the residual air exceeds 50 per cent or if the "ventilatory reserve" is 80 per cent or less [1-7 -c] When evaluating operative risk in the presence of a chronic "wet" bronchitis or marked bronchospasm, it is important that these tests of total pulmonary function be performed only after antibiotics, bronchodilators positive-pressure breathing, adequate rest, and postural drainage have been instituted

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tient who has had one lung removed for a bronchogenic carcinoma may be considerable In fact, this complication can lead to cor pulmonale with cardiac failure in one to five weeks, notwithstanding adequate blood oxygen saturation [1272g] This consideration must be borne in mind when resectional surgery is being planned, especially in the older patient with a peripheral tumor which might be removed by a procedure of lesser magnitude than a total pneumonectomy

Where facilities are available, valuable preoperative information about certain patients with bronchogenic carcinoma whose pulmonary function is in doubt might be obtained by determining the pulmonary artery pressures shortly after a trial occlusion of the main bronchus and the pulmonary artery on the affected side Brofman and his colleagues have set forth their extensive experience with the use of unilateral pulmonary artery occlusion as a test of pulmonary resection tolerance (p 823) [1 72t] While there may be some disagreement as to whether overinflation of the remaining lung following a pneumonectomy actually constitutes "emphysema," little doubt exists on the basis of physiologic studies *that the* dyspnea is accentuated by the further reduction in the lung compliance and that the overinflation necessitates increased respiratory work with exercise [1 7 h]

It is not generally appreciated that from the point of view of pulmonary function, pulmonary tuberculosis may be regarded as a localized disease with much normal lung tissue intervening On the whole, physiologic changes in pulmonary function can be detected only when at least three segments are involved Even then, however, it is possible to detect only minor disturbances in gaseous exchange along with some increased venous admixture [127 i] McClement has also pointed out that uncomplicated pulmonary tuberculosis—even when it is far advanced—has little influence on either the cardiac output or the resting and exercise pulmonary artery tension

It is not amiss to emphasize at this point that there is *no* substitute for the careful and detailed history, physical examination, fluoroscopic examination, interpretation of serial x rays, and emotional evaluation made prior to pulmonary function studies This is particularly true in ascertaining the physiologic status of elderly patients with bronchogenic carcinoma or tuberculosis who are being considered for resectional surgery The value of the comprehensive fluoroscopic study after *at least* twenty minutes of dark adaptation should not be relegated to a secondary status by ventilatory function studies Much vital information pertaining to the status of the diaphragm (position, excursions, rate of movement paradoxic motion), mediastinal shifts, the heart (right or left ventricular predominance, size and activity of the pulmonary artery segment), and the lungs themselves (particularly air trapping) can often be best achieved by such an examination

Carbon Dioxide Narcosis This complication is most apt to occur in the patient with extensive pulmonary emphysema, pulmonary fibrosis, or bronchiectasis Carbon dioxide retention and narcosis usually follow the institution of high concentrations of oxygen, which removes the hypoxic stimulus to the chemoreceptors

With regard to anesthesia, marked elevations in carbon dioxide tension following surgery are most commonly encountered in patients who were anesthetized with nitrous oxide and intravenous supplements [1278d] It may also result from the occasional prolonged apnea following the use of succinylcholine [1273] There are a number of possible explanations for the prolonged apnea that follows succinylcholine among which the following are the most likely (1) low plasma cholinesterase levels (particularly in patients with anemia, liver disease, malnutrition, and cachexia), (2) central respiratory depression by the combination of premedicant drugs, anesthetic agents and succinylcholine (3) prolonged passive hyperventilation, with an ensuing exhaustion of the Hering Breuer reflex and the lowering of the arterial carbon dioxide level below that necessary for stimulation of the respiratory centers, and (4) depression of the blood calcium ion levels as might be the case with the rapid infusion of large amounts of citrated blood [1278c]

Furthermore, the compensation that patients with chronic respiratory obstruction achieve while awake or naturally asleep is frequently lost when they are anesthetized [1264a] It has been shown that there is a reduction in the cardiac output, the total pulmonary vascular resistance and the pulmonary arterial hypertension in hypoxic patients with pulmonary emphysema upon breathing 99 6 per cent oxygen [1273b] In patients with reduced alveolar ventilation (emphysema asthma, severe kyphoscoliosis, extensive pleural disease), it is apparent that the use of carbon dioxide as a respiratory stimulant could lead to serious consequences

Pulmonocardiac Failure The considerable degree of cardiac strain in patients with extensive pulmonary disease kyphoscoliosis and other deformities of the chest cage is often not fully appreciated until quite late [876] The great sensitivity of these patients to narcotics cannot be overemphasized [880a]

Pulmonary Hypertension Not only does "primary" pulmonary hypertension predispose to effort syncope but death may follow such otherwise innocuous procedures as barbiturate anesthesia, the determination of circulation times and cardiac catheterization [873] [874] Reference was made earlier to the dire complications of the pulmonary arteriolar sclerosis secondary to prolonged pulmonary hypertension that may follow corrective cardiac surgery, particularly in the case of interventricular septal defects (p 443) [879c] Sudden death has occurred both postoperatively and post partum in patients with patent ductus arteriosus In most of these instances there was an unrecognized reversal of the flow of blood from the pulmonary artery to the aorta due to the development of increased pulmonary resistance and an ensuing pulmonary hypertension (p 286) [881c] The surgeon must search for an associated postvalvular constriction of the pulmonary artery at the time a pulmonic stenosis is being corrected since the two defects may coexist (p 276) [875c]

Pneumothorax A contralateral pneumothorax must be suspected when severe respiratory embarrassment occurs after the resection of a pulmonary cyst It is usually the result of a ruptured contralateral emphysematous bleb [L-75f] If unrecognized the patient runs the dangers attendant upon a tension pneumothorax collapse of the lung opposite to the opera

tive site, and marked mediastinal shifts Immediate thoracentesis followed by intrapleural catheter drainage is necessary

When a pneumothorax is accompanied by profound systemic collapse, particularly after previous endoscopic examination, rupture of the esophagus associated with a previously herniated stomach should be considered Pneumothorax has also been observed after brachial plexus or intercostal nerve blocks, and following operations below the diaphragm [1273c]

Subcutaneous and Mediastinal Emphysema The subcutaneous emphysema that results from the escape of air into the pleural space through a thoracotomy incision and thence into the extracostal tissues is usually self limited On the other hand, it could indicate the presence of a potentially serious tension pneumothorax due to significant bronchial or alveolar leaks The latter is particularly likely if the tension of the involved subcutaneous tissues is considerable The ability of a small mediastinal emphysema or pneumothorax to simulate acute coronary pain has been emphasized (p 265)

Evans and Smalldon have presented several instances of fatal postoperative mediastinal emphysema [1275a] They attribute this complication to the rupture of alveoli from the increased positive pressures employed in re inflating previously damaged lungs (i e , with pulmonary fibrosis, pulmonary emphysema and blebs, or evidence of bronchostenosis)

Mediastinal emphysema and pneumothorax have also been reported as unusual sequelae of tracheotomy,[1275b] tonsillectomy,[1275c] and operations on the neck [1275d] These complications result from the sucking of air into the mediastinum following violent respiratory movements through either the local wound the tonsillar bed, or along the carotid sheath, respectively Minor instances of mediastinal emphysema following the rigors of child birth are probably overlooked [1275e] It is apparent that when a tension pneumomediastinum is suspected to be interfering with the venous return, decompression by an incision through the suprasternal notch is indicated

Activation or Spread of Pulmonary Tuberculosis It has been repeatedly observed that there is a decided tendency among patients undergoing gastrectomies and other nonthoracic procedures to suffer activation of a previously quiescent pulmonary tuberculosis [1276a] Knowledge of this situation makes it extremely important to obtain preoperative chest films routinely, to restore patients who are less than 85 per cent of their standard weight to a satisfactory state of nutrition, and to closely follow apparently inactive lesions for as long as two years after surgery Tuberculosis may spread rapidly in a lobe whose major artery was injured or ligated during resectional surgery involving an adjacent lobe or section With the large numbers of resected lung specimens now available, experienced phthisiologists have become more aware of the fact that there is frequently no correlation between the activity of the lesion histologically and either the duration of sputum negativity or the appearance of the lesions by x ray

Even with the use of streptomycin, isoniazid and PAS there still exists a significant potential for spread that must always be borne in mind In one survey of patients with pulmonary tuberculosis who were subjected to 287 nonthoracic operations in the early antibiotic era the incidence of postoperative spread was 10 9 per cent [1276b] It is emphasized that once a

caseous or necrotic process has become established tuberculous chemotherapy may not be able to check the liquefaction and sloughing of the lesion.[1276c] The general experience concerning the early postoperative ambulation of tuberculous patients who have undergone resectional surgery has been favorable provided it is instituted gradually and over a longer period of time than is the case following other types of surgery.[127 d]

Bronchopleural Fistula. While the failure of proper bronchial closure is at times the basis of a bronchopleural fistula developing in the early postoperative period, sloughing of the suture lines can also be due to virulent pleural or mediastinal infection. Most bronchopleural fistulas following resectional surgery for tuberculosis are usually the result of small bronchial leaks from the raw surfaces of the lung rather than from the larger bronchi. Because of the lack of support of the intact costal cage, severe coughing may significantly contribute to this complication, even several weeks following an obliterative thoracoplasty.[1276d]

The shift from extrapleural collapse procedures to extraperiosteal plombage has obviated the serious complication of bronchoextrapleural fistula to a large extent.[1 7-a] Every experienced phthisiologist and thoracic surgeon has been lured in the past by "the siren song" of the extrapleural operation and plombage. All too often the ensuing heart breaking late complications of this procedure took place years later—at a time when total rehabilitation had apparently been achieved.[1 76] Infection, perforation, migration, and protrusion or extrusion of the foreign material has occurred whether the extrapleural plombage consisted of air, oil, paraffin, lucite spheres, ivalon, cellophane, or polythene.

The problems of tuberculous empyema and blown stumps after a pneumonectomy still continue to harrass even the most skilled surgeons. These complications tend to occur most frequently in the presence of drug resistant organisms. While a residual pleural space may be noted in as many as one third of patients in whom small resections for pulmonary tuberculosis are performed—even with the routine use of multiple chest catheters for subsequent negative pressure drainage of the pleura—the fate of the space is usually one of gradual resolution. Significant infection is encountered but rarely under these circumstances.[1276f] Should persistent air leakage occur after a subtotal pulmonary resection and prevent the early obliteration of the pleural cavity, constant strong suction will frequently suffice.[1 7 d]

Residual Stump Disease. When positive sputa are encountered following a pneumonectomy for tuberculosis, the possibility of a residual stump infection must always be considered. This issue assumes added importance in view of the great value of local measures and aerosol therapy.

Thoracoplasty Failures and Complications. Resectional therapy is indicated in the following instances of thoracoplasty failures: when the operation failed to close a cavity, when an apparently closed cavity subsequently reopened, when there is persistent positive sputum even when there had been apparent cavity closure, when there is an unobliterated empyema pocket, when there is apparent cavity closure and conversion of sputum but residual cough and expectoration (often due to the angulation of the bronchi and the atelectasis induced by thoracoplasty, particularly in the

presence of bronchiectasis), and when there is apparent cavity closure but profuse or recurrent pulmonary hemorrhage.[1276e]

A detailed discussion pertaining to the problem of the residual space following lobectomy or pneumonectomy will not be entered into here. Suffice it to point out that most thoracic surgeons no longer routinely employ "tailoring" thoracoplasties after the excision of tuberculous lungs. Neither the anticipated deleterious effect upon respiration, nor the recurrence of tuberculosis, that was at one time considered to be the potential sequela of overdistension of the remaining lung, has been generally encountered.

On the whole, this procedure is at present best reserved for the various complications of resectional surgery—most notably, a persistent space, leak, or fistula. There is much to recommend a limited thoracoplasty, however, inasmuch as little normal lung tissue is affected, no deformity results, and it may prevent or control excessive distortion of the trachea, bronchi and pulmonary vessels, bronchopleural fistula, and the induced postresectional cardiovascular strain resulting from excessive mediastinal shifts.[1276d] Experience has shown the wisdom of not performing a concomitant resection and thoracoplasty on a routine basis because of the great incidence of postoperative complications.[1276g] The postoperative course of such individuals can be very stormy, largely due to the paradoxical respiration and the difficulty encountered in proper expectoration.

Unusual Complications Following Thoracoplasty or Lobectomy. Although active physical therapy is usually instituted after thoracoplasty to prevent or to minimize certain musculoskeletal complications *involving the* chest wall, the thoracic spine, and the scapula or shoulder, little attention has been paid to the late development of a *scalenus anticus syndrome*.[1276f] The persistence of pain and numbness in the arm, shoulder, and neck of a patient who was subjected to this operation should lead one to consider this possibility, inasmuch as scalenotomy can often bring complete relief. It is conjectured that when this complication occurs, the brachial plexus *or its roots are compressed by the taut fibromuscular band that* develops after the scalenus anticus muscle is stripped off the scalene tubercle.

In addition to an empyema necessitatis and a cold abscess resulting from tuberculous involvement of either the spine or a rib, the possibility of a *pulmonary hernia* should be considered in the post-thoracoplasty patient who demonstrates persistent intercostal or axillary pain, together with a pulsion mass of the chest wall.[1276h] The development of *contralateral fractures* of the first and second ribs following the first or second stages of a thoracoplasty is usually asymptomatic. It is mentioned because an erroneous diagnosis of spread might be made as a result of the shadow cast by the ensuing callus.[1276i] While rare, a *Horner's syndrome* due to trauma involving the cervical sympathetic system can complicate these procedures, particularly when accompanied by apicolysis.[1276j] The author is familiar with one case in which a lobectomy was followed by the development of an inner chest wall mass at the operative site which proved to be a *benign keloidal tumor*. Extra abdominal desmoid tumors of the thoracic wall have resulted from other forms of trauma to the chest.[1058d]

Pendular Motion of the Mediastinum. The significance of mediastinal

shifts is cited several times in this chapter There are a number of causes for such movements, including endobronchial stenosis and obstruction of the smaller bronchioles, pneumothorax, bullous emphysema, pleural effusion or thickening a paralyzed diaphragm, and the parenchymal disease itself Samet and Anderson have pointed out the superiority of fluoroscopy over radiography in visualizing these shifts [1275k] They classify the pendular movements as follows

Types I and II	The mediastinum is midline on expiration, but is displaced to one side during inspiration
Type III	The mediastinum is displaced to one side on expiration, but to the opposite side during inspiration
Type IV	The mediastinum is midline on inspiration, but is displaced toward the normal side on expiration
Type V	The mediastinum is pulled to the diseased side during both phases of respiration as a result of complete endobronchial occlusion

Paradoxical Motion of the Chest Wall This complication follows fractures of several ribs or the excessive decostalization in extrapleural thoracoplasty A considerable strain is thrown onto both the cardiac and pulmonary reserves It also renders the cough ineffective and enhances hypoxia and carbon dioxide retention

Rupture of the Esophagus This catastrophe is occasionally quite atypical in its onset In such instances it has been initially considered as a medical problem especially myocardial infarction pancreatitis, and pulmonary infarction [1277] Its presence is suggested by the occurrence of marked vomiting severe pain in the chest and upper abdomen (usually on the left side), dyspnea prostration hydrothorax or hydropneumothorax (most frequently on the left) and subcutaneous or mediastinal emphysema (often first apparent as subcutaneous emphysema in the suprasternal notch) Vomiting need not always be present however

Naclerio has noted the characteristic 'V sign" which may serve as a valuable early clue to the diagnosis of a ruptured esophagus [1277c] This consists of a localized emphysema in the lower mediastinum that assumes the form of the letter 'V (this configuration corresponding to the fascial planes of the mediastinal and diaphragmatic pleurae in the region of the lower esophagus) This complication must be suspected when severe collapse or a bizarre history of something bursting in the chest follows endoscopic examination bouginage, or an increase in the intra abdominal pressure postoperatively

Anesthetic Problems with Particular Reference to the Presence of Extensive Pulmonary Disease There is a wide variation in the choice of anesthetic agents and techniques that can obviously be used with great success in poor risk cardiac and pulmonary patients depending upon the experience and the preference of the individual anesthetist Experience has clearly demonstrated that the wisest choice of an anesthetic agent in difficult situations usually follows a deliberate discussion of the potential risks and unique problems of the particular patient between the surgeon the internist, and the anesthetist

It is not amiss to cite briefly the following advantages of ether over cyclopropane and other anesthetic agents in thoracic surgery at this point it is tolerated better by a crippled circulatory system, it can be used with an abundance of oxygen (more than 95 volumes per cent), respiration is not depressed at levels which produce good muscular relaxation, it does not tend to produce respiratory acidosis, and finally, it is associated with the lowest mortality rate [1263]

The main disadvantage of the use of ether in patients with respiratory disease is the delayed recovery that is apt to ensue following prolonged surgery [1278a] Since ether tends to produce more secretions than the anesthetic gases, the latter are preferred in the presence of a suppurative "wet lung" The use of thiopental, cyclopropane, curare, and morphine is usually contraindicated in the patient with bronchial asthma because of the ever present danger of bronchospasm

A respiratory acidosis is frequently associated with anesthesia, largely *due to the elevated alveolar carbon dioxide tension levels This rise* is accounted for in part by the position of the patient, the increase in the respiratory dead space, hypoventilation, the effect of the endotracheal tube, and possibly the action of the anesthetic agent on the bronchiolar musculature [1263] It is possible that the fall in blood pressure following various surgical procedures is related in large measure to the removal of the stimulant action of the carbon dioxide as its tension becomes reduced and as the pH rises This is particularly true in the case of "cyclopropane *shock*" [1278b]

In patients with emphysema and other respiratory disorders, barbiturate anesthesia may cause the respiratory center to become so insensitive to alterations in carbon dioxide tensions that respiration must be maintained chiefly by the chemoreceptors of the aortic and carotid bodies [1278a] *Although preoperative medication with promethazine* hydrochloride has become quite prevalent and useful, it incurs the potential danger of respiratory depression when thiopental sodium or morphine are subsequently administered

Perhaps one of the most important periods with reference to the safety of the anesthetized individual is in *the immediate postoperative state* before his transfer to the recovery room Dripps has ably described a number of these hazards [1278e] Arterial hypotension may precipitously occur as a result of the change in the patient's position, reduction in the level of the general anesthesia (as exemplified by "cyclopropane shock") unrecognized or inadequately treated blood loss (especially after procedures on the lungs, prostate and pancreas where fibrinolysins may be introduced), and embolism (thrombi, fat, or air) Respiratory obstruction or depression might be produced in this period by soft tissue obstruction, laryngospasm or vocal cord paralysis following removal of the endotracheal tube, vomiting, unrecognized pneumothorax or atelectasis, tight surgical dressings (as after a mastectomy), the respiratory depression of the muscle depressants, and a "diffusion anoxia" The last is most apt to occur after nitrous oxide anesthesia as this gas moves into the alveoli and the blood stream by virtue of its great solubility In the process, the residual oxygen is diluted Finally, there may be considerable pain or restlessness in the *immediate*

postoperative period The agitation represents one phase of the patient's recovery from anesthesia It may be so great, however, as to require medication which in itself could produce retching, vomiting hypotension, or other undesired effects

Tracheitis Sicca This condition poses a serious complication in patients who have recently been subjected to a laryngectomy or to the insertion of a tracheotomy tube While it may occur at any time following either of these procedures, it is particularly prone to take place during the winter months This disorder is characterized by the production of crusting, ropy secretions, and an eroded bleeding tracheal mucosa in the more severe cases A vicious circle takes place, with coughing and dyspnea accentuating the drying process and producing further cough and dyspnea An actual intimate cast of the trachea may form The use of pancreatic dornase as a fine spray via a polyethylene catheter has produced the most encouraging results to date in this condition [1279a]

Retropleural Hematomas Following Sympathectomy It is important to be aware of the roentgenologic variations caused by extrapleural effusions that may be encountered in up to one fifth of patients following operations on the sympathetic nerves of the neck and the trunk This diagnostic problem can assume greater proportions when neither the site of the rib resection nor the clips are visualized The retropleural hematoma usually appears as a smooth bordered or slightly lobulated homogeneous mass that is contiguous with the posterior thoracic wall [1279b] While this is a benign condition it might be mistaken for a neurofibroma, or mediastinal and pulmonary disease

Severe Intrathoracic Hemorrhage Associated with Thoracotomy The surgeon is apt to encounter this serious situation when the chest is opened for a presumed solid mediastinal or pulmonary tumor that proves to be a vascular lesion The value of angiocardiography in avoiding such situations was pointed out in an earlier chapter (p 336) Similarly, if the surgeon is not aware of the nature of the anomalous vessel that is producing a bronchopulmonary sequestration fatal hemorrhage might ensue in the course of a thoracotomy (p 130) [458]

Radiation Pneumonitis The possible role of postoperative radiation in the production of unusual lung changes following breast, pulmonary, esophageal, or chest wall surgery for malignant disease was discussed in Group XIII (p 398) [1198, 1200] The severity of the reaction in the lungs is not only dependent upon the rapidity of treatment, the total dosage and the volume of tissue irradiated, but also upon the patient's age and the pathologic processes within the pulmonary parenchyma (especially metastases and intercurrent infection) Radiation over the hilus is more prone to result in extensive fibrosis than when the therapy is directed over the periphery of the lung

Mention is made of the significant role played by the impairment of alveolar capillary diffusion in the functional abnormalities observed and of the wide variety of pathologic processes that might be simulated in the chest films most notably that of idiopathic interstitial pulmonary fibrosis In the absence of fibrosis and atelectasis an elevation of the diaphragm with subsequent blurring and indistinctness of its outline poses an early

roentgenographic clue to this reaction Furthermore, the relative stability of a pneumonitic process in serial roentgenograms over a subsequent period of two or more years tends to preclude the diagnosis of a neoplastic spread

RENAL COMPLICATIONS

Chronic Nephritis and Uremia These conditions can remain asymptomatic for prolonged periods, particularly if adequate fluid is presented to the kidneys Since impaired renal function may be difficult to diagnose on the basis of only one preoperative urinalysis and NPN, it must be actively considered when managing elderly patients, both before and after surgery [174] Fortunately, there has been an optimistic re-evaluation of the risk and operability of many patients with chronic renal disease and mild azotemia in recent years This orientation stems largely from our ability to anticipate and cope with the majority of derangements that might arise Furthermore, it has been observed that *patients with chronic renal disease appear to tolerate marked derangements in the chemical composition of their body fluids much better than do patients with acute renal failure* This apparent paradox is presumably due to their longer period of adjustment [1800]

In line with the previous remarks, it is stressed that all too often there are treatable extrarenal factors which contribute to the rapid deterioration of renal function in surgical patients, but which are casually and incorrectly attributed to "poor renal reserve ' Some of these influences include dehydration catabolic activity, infection, salt depletion, urinary tract obstruction (even when the urine volume appears to be adequate), and hyperkalemia or hypokalemia

Pyelonephritis and Necrotizing Renal Papillitis These diagnoses always merit emphasis in the postoperative patient who is severely ill from unexplained cause This consideration is most imperative in diabetics, in those patients with obstructive uropathies and following instrumentation upon the urinary tract (p 110) [388, 389, 394] A pre existing chronic glomerulonephritis pyelonephritis, or polycystic renal disease may suddenly deteriorate into an oliguric phase with fulminant renal failure because of intercurrent infection, instrumentation, excessive vomiting, or other metabolic disturbances [391]

Acute Tubular Necrosis or Necrotizing Nephrosis (previously erroneously called 'lower nephron nephrosis') This condition is likely to occur when a shocklike state or an impaired renal blood supply exists Massive trauma, head injury, extensive hemorrhage, severe fluid loss, transfusion reactions, acute pancreatitis, massive pulmonary infarction, severe infection (especially peritonitis), and severe anoxia are the most *significant* precipitating factors [1 80]

Acute renal failure may also result from various medical and surgical complications within the urinary tract (p 54) Specific mention is made of stricture, ligation, or calculus occlusion of the ureter from one kidney when the other is absent or nonfunctioning The formation of a large retroperitoneal hematoma or of a hemorrhage into the broad ligament following pelvic surgery may produce ureteral angulation of a sufficient degree to

obstruct the ureters [180] Other postoperative complications leading to acute urinary tract obstruction include the occlusion of the ureteral orifices following total prostatectomy, and the ureteral injury in patients who are subjected to panhysterectomies (*vide infra*)

It is emphasized that there is no substitute for the careful examination of the urinary sediment from freshly passed urine in establishing the diagnosis of renal tubular necrosis This emphasis is especially pertinent when the acute nephropathy is due to a transfusion reaction The finding of hemoglobin and fat casts—in addition to a low specific gravity—will conclusively establish this diagnosis should any doubt exist (as when the possibility of simple dehydration is entertained) Intravenous pyelography should always be deferred in the presence of acute urinary suppression

With the careful regulation of fluids, calories infection, and potassium and other electrolytes, patients with acute tubular necrosis can recover even after three to four weeks of profound oliguria In view of the possible nephrotoxic effect of marked hypokalemia, it might be necessary to paradoxically administer potassium in the oliguric phase of acute tubular necrosis should this unusual electrolytic combination be encountered [1 81b] Severe shock or hypoxia frequently induces prolonged damage to the renal function, as manifested by persistent cylindruria and isosthenuria for many months

Another cause of intravascular hemolysis leading to renal shutdown that is unique to the field of urology stems from the irrigation of the lower urinary tract with plain distilled water following a transurethral prostatic resection [1281a] The induced hemoglobinemia and hemoglobinuria are apt to be overlooked because of the concomitant postoperative hematuria

Physicians must resist the temptation of introducing an indwelling catheter in the conscious patient with acute postoperative renal tubular necrosis The danger of infection under these circumstances is too great to justify the little that is gained by such a procedure Most of these individuals are actually able to void by themselves When they are unable to do so, bladder percussion for distention will usually indicate the onset of the polyuric phase

The following considerations should be entertained in the management of patients who are in the diuretic phase following acute renal failure (1) the nonprotein nitrogen level is apt to rise at this time, notwithstanding the passage of large quantities of urine by the patient and (2) since the excessive loss of both sodium and chloride in the urine often represents the fluids and electrolytes that were administered in excessive amounts during the oliguric phase replacement therapy may not be necessary or desirable [180]

In recent years, we have become aware of the much more common "formes frustes of lower nephron nephrosis as manifested by the accidental discovery of a slightly elevated postoperative NPN in the absence of oliguria This complication is usually quite benign with the mild azotemia disappearing after several weeks In certain instances of tubular necrosis where the oliguric phase is either very short or absent and where the tubules are able to retain salt and to excrete a dilute urine which con

tains a low concentration of electrolytes, the finding of a very low concentration of urea in the urine might aid in the diagnosis [1281b]

The Problem of "Reflex Anuria" The severe oliguria or anuria and the rapidly developing azotemia that occasionally complicate *ureteral catheterization*, especially during the course of retrograde pyelography, can be differentiated from acute tubular necrosis by (1) absence of shock, intravascular hemolysis, severe trauma, hemorrhage, and nephrotoxins, (2) rapid and marked rise in blood pressure, (3) absence of a fixed low specific gravity in the urine recovered during and after the ureteral obstruction has been relieved, in contrast to the situation in acute tubular necrosis, (4) the more impressive manifestations of an acute urinary tract infection (fever leukocytosis pyuria costovertebral angle tenderness), and (5) great fluctuations in the volume of urine recovered from one day to the next

Recystoscopy in a number of these patients revealed the presence of a bullous edema involving the ureteral orifices This phenomenon could readily account for the obstruction, since insertion of ureteral catheters effected a cure [1281d] The edema was explained as a reaction to the local trauma, to the formaldehyde used in the sterilization of the catheters, or to the contrast medium employed

Urinary Tract Complications Following Radical Hysterectomy and Pelvic Lymphadenectomy Two serious complications may occur, related in large measure to the induced interference with the blood and nerve supply to the distal ureter and the urinary bladder These consist of vesicovaginal or ureterovaginal fistulae and stricture of the terminal 4 to 5 cm of the ureter, resulting in hydronephrosis and loss of renal function Perforation of the ureter should be suspected when sudden pain in the back radiating to the inner thigh or the suprapubic area or unexplained high fever occurs one to two weeks postoperatively [1281e]

Acute Renal Failure in Pregnancy Several types of severe nephropathy may singularly complicate the course of the pregnant patient In the majority of these cases, the lesion is one of an acute tubular necrosis, usually subsequent to uterine hemorrhage or intravascular hemolysis [1 82] It is aggravated by potassium intoxication Renal cortical necrosis can complicate severe abruptio placentae, particularly in multiparous women over the age of thirty Patients are known to have recovered from bilateral cortical necrosis of the kidneys [180c] Potassium depletion secondary to hyperemesis gravidarum or the loss of this electrolyte in pyelonephritis must also be borne in mind

Nephrectomy of a Sole Functioning Kidney It is never superfluous to warn against performing a nephrectomy on a traumatized or atrophic kidney until the full status of the other one is definitely known [1243] [1244] It may be almost impossible to accurately differentiate between congenital hypoplasia chronic "atrophic pyelonephritis and a chronic atrophic" pyelonephritis superimposed upon congenital hypoplasia as the cause of a unilaterally small kidney either clinically, urographically, or pathologically [1 83]

Renal Tract Complications of Prostatism and Prostatic Surgery The frequency with which middle-aged and elderly men—either with manifest

or unrecognized prostatic disorders—are thrust into acute urinary retention by the administration of parenteral fluids or by the mercurial diuretics in the usual dosage is impressive [194] A prostatitis may also occur The problems relating to the difficulties in diagnosing 'silent prostatism and the profound fluid and electrolyte disturbances in these patients were discussed in Group II (p 56) [190 193]

One should be aware of the entity of *osteitis pubis* following a supra pubic or retropubic prostatectomy in order to avoid mistaking it for either an infection in the prevesical space or a metastasis [1 84b] Attention to the delayed onset of symptoms, the distribution of the pain, and the periosteal reaction by x ray can avert such errors

Urinary Extravasation This is a most serious situation that should be suspected following urinary tract surgery or trauma, or in patients with urethral strictures who exhibit unexplained fever and toxicity Prompt drainage of the area is mandatory

Atheromatous Emboli to the Kidneys after Aortic Surgery This diag nosis is suggested by the development of a relentless uremia with anuria or severe oliguria after surgery for either an aneurysm or an atherosclerotic occlusion of the abdominal aorta This entity is discussed at greater length elsewhere in this chapter (p 444)

HEMATOLOGIC COMPLICATIONS

Transfusion Reactions Since there still exists a mortality of one pa tient per 1000 to 3000 transfusions, the unnecessary use of whole blood as a postoperative tonic is to be deplored The other sequelae include anaphylactic reactions bacterial contamination (*vide infra*) hemolytic reactions due to incompatible blood air embolism (p 444) citrate intoxication (p 462) febrile reactions the transmission of infectious disease sec ondary hemochromatosis (p 61) ammonia intoxication,[1 95] hyperkalemia and circulatory overloading [1 85 1 87] Even in the operating room area blood should not be allowed to remain at room temperature for any period of time

In addition to meticulous typing and cross matching the use of plasma or plasma expanders packed red blood cells slow infusions pretransfusion antihistaminics and fresh blood may obviate many of these reactions in selected patients The thrombocytopenia occurring after massive transfusions (especially when in excess of 14) has been attributed both to the dilution of the recipient s blood with nonviable platelets and to a possible platelet depressing factor that is frequently present in the plasma of stored blood [1286 d] It can be obviated under the e circumstances by the use of fresh blood The development of purpura following the infusion of apparently compatible blood in a patient who had not previously received blood and who was not allergic to any drugs should raise the possibility of platelet antibodies being present in the donor blood In one such instance the donor was found to have sarcoidosis [1 84]

It is the general experience that subclinical sensitization and trans fusion reactions can take place in the absence of demonstrable incompati bility—even with the sensitive and usually reliable Coombs test Accord

ingly, "complete" blood typing (i e, in the A-B O, Rh, M N S, Kell, Duffy, and Kidd blood group systems) may be in order in certain patients who might require long term transfusion therapy, as could be the case in hemophilia, aplastic anemia, and Cooley's anemia [1286b] Weak reactions in the cross match test must not be disregarded When any doubt exists, the biologic cross match test is indicated (p 826) This consists in checking the free plasma hemoglobin ten or fifteen minutes after a small amount of the donor blood is administered for levels in excess of 10 mg per 100 ml

In recent years, a significant body of evidence has been gathered to implicate the development of isoantibodies against the white blood cells (and probably the platelets) as a cause for febrile transfusion reactions [1286c] This is particularly true in patients who have received many transfusions since the donor leukocytes are effective antigens It is possible to prevent such reactions by the pretransfusion removal of the buffy coat from the donor blood

The Problem of Contaminated Blood The transfusion of small volumes of infected blood can produce a picture not unlike that of severe protein shock, with circulatory failure and a rapid demise [1288a] Collected blood can be variously contaminated at the site the phlebotomy needle is introduced through the donor s skin, at the site the piercing needle of the donor set enters the rubber stopper and within the path of blood left in the diaphragm by the puncture tract Inasmuch as contaminated blood cannot be identified by mere inspection of the specimen and since the intrinsic bacteriostatic properties of blood begin to diminish after one week of refrigeration, culturing techniques are necessary for the recognition of contamination These methods must be able to cover a wide temperature growth range in order to detect psychrophilic organisms, and yet be practicable The problem of infected stored blood will undoubtedly increase because of the technical feasibility of storing blood for longer periods due to the improved methods of blood preservation

Two of the chief problems that were heretofore encountered consisted in (1) the obtaining of false negative cultures from blood that was collected in conventional glass bottles, and (2) the opportunity for contamination that exists during the very procedure of procuring a sample for culture Walter, Kundsin, and Button have described a method that has been in use for several years at the Peter Bent Brigham Hospital which appears to have surmounted these difficulties [1288b] The donor tube used is actually an integral part of the storage container It can be hermetically sealed and cut off in segments to yield aliquots for bacterial culture without incurring the risk of exposing the residual blood to contamination

Citric Acid Intoxication This relatively infrequent complication tends to occur when multiple transfusions of citrated blood or plasma are rapidly administered It is a particularly potential hazard in patients undergoing cardiovascular surgery and in individuals with either liver disease or mechanical obstruction to their hepatic circulation [1 89] In the former instance, electrocardiographic monitoring may be most helpful in detecting citrate intoxication since the muscle tremors and tetany resulting from the depressed ionized serum calcium levels are usually absent in the presence of deep shock or surgical anesthesia The induced changes consist of a

prolongation of the Q-T interval depression of the ST segment, delay in interventricular conduction, a progressive fall in the systemic and right ventricular pressures (that does not respond to the further infusion of citrated blood), and finally cardiac arrest [1-59b] These effects can be promptly reversed by small amounts of calcium chloride

Operative and Postoperative Bleeding When abnormalities in the clotting mechanism are found, they tend to consist of combinations involving a decrease in either the fibrinogen prothrombin, factor V or factor VII, and fibrinolysis [1291b]

Another cause of postoperative bleeding may be *vitamin K deficiency* resulting from deficient diet in a chronically ill patient, liver disease and prolonged administration of oral antibiotics [1291i] The last causes reduction of the bowel bacterial flora with a decrease in bacterial synthesis of vitamin K The low level of prothrombin is apt to be accompanied by a decrease in Factor VII (proconvertin serum prothrombin conversion accelerator) and the plasma thromboplastin component (PTC)

A hemostatic defect accompanies the use of *dextran* as a plasma volume expander, especially in patients who either have a tendency to bleed or who have received many transfusions of whole blood In 8 per cent of 163 *normal* individuals who received 1 liter of 6 per cent dextran the bleeding time exceeded thirty minutes with the maximal effect occurring in from three to nine hours [L-91i] (No dilution or reduction of the fibrinogen or platelets could be demonstrated) A comparison of dextran preparations indicates that the hemostatic derangement is directly related to the employment of those with the highest molecular weights

Hyperheparinemia with or without Thrombasthenia The subject of hyperheparinemia is still one of considerable controversy Nevertheless, the successful use of protamine sulfate (intravenously or intramuscularly) and of desoxycorticosterone (intramuscularly or in the form of linguets) in patients with hemorrhage occurring pre- or postoperatively and in the postpartum stage renders the consideration of such a possibility of some importance [1290a] Furthermore in a patient with marked hyperheparinemia studied by Quick and Hussey cortisone and fresh frozen plasma permitted the extraction of teeth without abnormal bleeding [L-90b] The thrombin time test as an aid in both diagnosis and following the course of therapy was of great value in their hands

In addition to the increased blood heparin titer during the hemorrhagic phases Bell and Imber have observed the following derangements or characteristics in 27 patients with a thrombasthenic syndrome normal clotting time normal venous platelet count low normal adhesive platelet count prolonged oil clot retraction time decreased serum prothrombin time prolonged bleeding time and an abnormal tourniquet test [L-90a] Females with this disorder are encountered twice as frequently as are males

Fibrinolysis Fibrinolytic purpura has occurred in operations upon the prostate the lung and the pancreas, in malignancy involving these organs in shock burns and transfusion or anaphylactoid reactions, in acute leukemia and in severe liver disease [1-91] Defibrination can occur without lysis, but there is usually an associated reduction in fibrinogen and prothrombin The easiest and best test for this disorder is the determination

of the clot retraction time (p 678) A potentially useful semiquantitative method for the determination of the fibrinogen content in a sample of oxalated blood by the addition of Fibrindex (Ortho) is available[1291e]

The use of serum albumin and fibrinogen (in an attempt to neutralize the proteolytic enzyme) and of cortisone or corticotropin (to increase the circulating antienzymic effect) has been suggested in cases of postoperative fibrinolysis[1291e] On the other hand, the administration of excessive amounts of plasma fraction 1 for postoperative hypofibrinogenemia—even in the presence of a demonstrable fibrinolysin—can result in widespread intravascular fibrin deposition, thrombosis, and visceral infarction[1291f]

Afibrinogenemia is occasionally encountered as an added pathologic counterpart in several complications of pregnancy The latter include severe premature separation of the placenta, amniotic fluid embolism, long standing retention of a dead fetus *in utero* (most commonly in association with a high titer Rh isosensitization), convulsive eclampsia, criminal abortions, and postpartum hemorrhage[1291c] Acute tubular necrosis and bilateral renal cortical necrosis are the causes of death in one third of these patients—in large measure resulting from the associated shock When precipitous, the sudden intravenous infusion of such thromboplastin containing fluid may produce amniotic fluid embolism and a widespread occlusion of the terminal arterioles On the other hand, the circulating fibrinogen may be gradually depleted over a period of several weeks, in which case the predominant manifestation is hemorrhage of uncoagulable blood[1291d]

The release of thromboplastin into the maternal circulation that is associated with the cellular damage occurring in abruptio placentae and due to the prolonged retention of a dead fetus brings about massive intravascular clotting by the conversion of fibrinogen to fibrin (the "fibrinogen fibrin conversion syndrome") In effect, such massive defibrination (and also fibrinolysis) results in the circulating fluid portion of the blood representing virtually serum rather than plasma for all practical purposes The expanding hematoma in premature separation of the placenta contributes to the evolution of this syndrome by (1) extracting thromboplastic material from the placenta and the other decidual elements, (2) exposing the maternal uterine sinusoids in the course of its dissection and (3) providing the necessary hydrostatic pressure to force the thromboplastic material into the maternal circulation[888a]

Rosenthal has set forth a number of pertinent therapeutic considerations in the management of these patients which are still not generally appreciated[888a] Since shock *per se* will perpetuate the depletion of fibrinogen, this state must be promptly counteracted both by the use of very fresh blood (which will also restore the other depleted coagulation elements) and pressor agents When the fibrinogen loss is rapid and massive one cannot hope to restore the blood level solely with whole blood (which contains only approximately 750 mg per pint) Consequently, the use of concentrated fibrinogen preparations must be resorted to—or lacking this material, the use of concentrated dried plasma (i e , not restored to its full volume) Once the fibrinogen level has been repleted, the obstetrician can then concern himself with rupturing the membranes, administering pitocin, or performing either a hysterotomy or a hysterectomy, as the case demands

Even when considerable shock was present, a spontaneous restoration of the fibrinogen will usually take place within several days following the termination of the pregnancy

Postsplenectomy Thrombocytosis The degree of postsplenectomy thrombocytosis is unpredictable Nevertheless intravascular thrombosis infrequently results from the rebound thrombocytosis that follows a splenectomy which is performed for various indications Anticoagulants might be administered if the platelet level exceeds one million, and if the patient cannot be ambulated early or will remain incapacitated for a considerable period (Certain authorities, such as Welch and Dameshek do not subscribe to the use of anticoagulants [129])

When a splenectomy is performed for a myeloproliferative syndrome (myeloid metaplasia) on good clinical grounds two important complications often take place These are infection (particularly when large doses of the adrenocortical steroids were administered) and profound intravascular thrombosis In view of the sudden flooding of the circulation with very thrombogenic platelets, anticoagulant therapy for several weeks would appear to be indicated here [739]

Other Considerations Relating to Splenectomy and Thrombocytopenia Reynolds and Etsten have reviewed some of the anesthetic problems attendant upon splenectomy in 205 patients with blood dyscrasias including many instances of congenital spherocytosis acquired hemolytic anemia, thrombocytopenic purpura and either pancytopenia neutropenia or aplastic anemia [129 b] Complications and postoperative deaths were most frequent in the group with purpura in whom splenectomy was often of no therapeutic value Consequently, in the operative and anesthetic management of such individuals, the following considerations arise (1) the choice of anesthetic should depend more on the basis of the patient's liability to hemorrhage and hypotension than on the splenic contractility the agent produces, (2) endotracheal and intestinal intubation should be avoided when a thrombocytopenia exists (3) the blood volume should be maintained with adequate transfusions of fresh whole blood and (4) in the presence of an acquired hemolytic anemia infusions must be made with caution to avert severe hemolytic reactions

The development of simplified methods for preparing platelet concentrates without resorting to the use of refrigeration or special anticoagulants, has not only offered a means of controlling thrombocytopenic bleeding but has made it possible for patients with severe chronic thrombocytopenia to undergoe major surgery [129c]

Hematologists and surgeons alike should take cognizance of the fact that the overt manifestations of disseminated lupus erythematosus have appeared for the first time following splenectomy on patients who exhibited either an autoimmune hemolytic anemia or 'idiopathic thrombocytopenic purpura This situation might develop even when the preoperative L E cell tests were negative [938]

In the surgical patient with congenital spherocytosis who also has gallstones, the spleen should be removed first If complications should occur following a cholecystectomy which necessitate cessation of the operation a crisis will probably be precipitated if the spleen was not removed The

finding of Howell Jolly bodies in the red blood cells usually establishes the completeness of a previous splenectomy

Postoperative Anemias The development of megaloblastic anemias following extensive gastric resections, anastomoses with residual blind loops of bowel, gastrocolic fistulae, and the creation of intestinal strictures was discussed in Group VI (p 191) Due to the absence of hydrochloric acid resulting from an extensive gastrectomy, an iron deficiency anemia might also ensue Such an anemia is in part explained by the patient's inability to convert ferric hydrochloride to the ferric ion before reduction to the absorbable ferrous state can occur

HEPATIC COMPLICATIONS

Jaundice Many of the considerations that occasionally confront attending physicians and their medical and surgical consultants in the evaluation of obscure cases of jaundice were presented in Group III (pp 88–91) Several of these are further briefly amplified here The problems of portal vein occlusion and infarction of the liver following inadvertent ligation of the hepatic artery will be considered later in this chapter (p 485)

Postoperative jaundice is often due to the combination of the increased hemolysis attendant upon the transfusion of much blood and the impairment of liver function by surgical trauma, transient shock, and anesthesia [1294] The utilization of plastic bags containing blood for pressure transfusions during cardiac and vascular surgery to replace large amounts of blood loss can obviate much of the postoperative jaundice in cardiac patients with congestive hepatomegaly or cirrhosis [1294b]

Homologous Serum Hepatitis The incubation period prior to the onset of clinical jaundice may be as long as six months This interim is often characterized by insidious lassitude, anorexia, vague abdominal or flank aching, headache, and loose bowel movements [335] The potential sources of infection before, during, and after surgery are legion They involve not only the administration of blood products but also the introduction of the virus by infected needles, syringes, and lancets

Pylephlebitis The symptom complex of chills, fever, and mild jaundice following appendicitis and other forms of sepsis involving the areas drained by the portal system is less frequent now with the use of antibiotics It is still overlooked, however, even in the presence of these manifestations [1293]

Unrecognized Liver Disease Patients with severe disturbances in hepatic function—especially when unrecognized—tolerate surgery and anesthesia poorly [1 62] Irreversible failure is apt to ensue following any significant period of starvation [332] Prolonged hypoxia or shock may leave serious hepatic damage in its wake There may be profound fatty metamorphosis of the liver during pregnancy (p 93) [343]

Elevated Blood Ammonia Levels Following Portacaval Shunts Patients who are subjected to this surgical procedure may exhibit episodic stupor either spontaneously, or subsequent to the administration of a high protein diet, intravenous protein hydrolysates, ammonium chloride, methionine, or ammonium resins The underlying elevated blood ammonia level is related

not only to its defective extraction by the liver, but more significantly to the shunting of blood around the liver with removal or binding of the substance by the peripheral tissues (p 97)[350, 354, 1295] Since a marked increase in ammonia concentration occurs in blood during storage, it is wise to avoid the use of old bank blood in transfusing patients with severe liver disease and impending coma[1295b]

INFECTIOUS COMPLICATIONS

Evaluation of a High Postoperative Fever The following general scheme, based on the timing of the fever, has been of considerable value *First three days* temperature, pulse, and respirations all increased simultaneously—probably atelectasis or pneumonitis *Fourth to sixth day* pulse moderately elevated, respirations normal—probably a nonpulmonary infection (renal incisional peritonitis from the leakage of suture lines or a duodenal stump pelvic abscess subhepatic abscess subphrenic abscess) *One week* tachycardia out of proportion to the fever—thrombophlebitis and embolism

Vascular Collapse due to Infection In the presence of unexplained postoperative shock considerable attention must be directed to certain types of infection which are frequently not recognized as such This is in some measure due to the fact that the usual responses to infection may be masked, being replaced by a cold pale and sweating skin diminution of the peripheral pulses and cardiac output, and diminution of the systolic and pulse pressures High rectal temperatures can usually be obtained It is unlikely that adrenocortical insufficiency is primarily the basis for these phenomena They probably represent intense vasoconstriction and pooling of large quantities of blood in the splanchnic bed (p 165) Particular reference is directed to the following entities

PSEUDOMEMBRANOUS ENTEROCOLITIS While this form of enterocolitis was encountered prior to the antibiotic era and is occasionally observed in the absence of antibiotic therapy[493] it is distinctly more frequent now This entity has become an important cause of unexplained toxicity and shock following recent abdominal surgery including cesarian section[491, 494] The overwhelming toxemia associated with a micrococcic enteritis should be suspected after surgery in the patient who suddenly exhibits unexplained tachycardia, fever ileus diarrhea anemia hypoproteinemia, shock and oliguria between the second and seventh postoperative days This complication can also be observed postpartum following an abruptio placentae that was characterized by profound hemorrhage and shock[495] Diarrhea need not necessarily be present, however It is frequently (but not invariably) related to the development of resistant strains of staphylococci resulting from previous antibiotic therapy (Also see pp 140 and 153)

GRAM NEGATIVE BACTEREMIA Bacteremic shock caused by these organisms is an important complication of surgery or instrumentation especially when dealing with the genitourinary tract (i e transurethral prostatic resection cystoscopy p 164)[597, 600] Cirrhosis of the liver and diabetes mellitus appear to increase susceptibility to this type of bacteremia In a

series of 137 such cases, *Escherichia coli* and *Aerobacter aerogenes* were the responsible organisms in 100 patients[597] Even in the absence of aspiration, *E coli* may invade the respiratory tract during the course of therapy with penicillin or other antibiotics

BACTERIAL CONTAMINATION OF TRANSFUSED BLOOD The transfusion of small amounts of infected blood can produce a picture not unlike that of severe protein shock, with circulatory failure and a rapid demise[1, 88] This complication was discussed at length earlier in this chapter (p 462)

NECROTIZING RENAL PAPILLITIS The significance of this entity as a postoperative complication was elaborated upon under the section on renal complications (p 458) It should again be emphasized that this possibility must be considered in the patient with diabetes mellitus or obstructive urinary tract disease whose condition rapidly deteriorates in the postoperative stage without obvious cause[388, 389, 394]

Staphylococcal Infections With the undeniable increase in the incidence of hospital personnel who are carriers of pathogenic and antibiotic resistant staphylococci postoperative infection with these organisms has become a pressing problem (p 153) The mortality is particularly significant because the bacteremia frequently occurs in patients with diabetes mellitus, arteriosclerosis neoplastic diseases, and a variety of debilitating illnesses[491, 549, 550] This is especially true in the case of fulminating staphylococcal pneumonias (p 121) When a puerperal mastitis or breast abscess due to the staphylococcus is encountered one should be cognizant of the possibility that the infant acquired this infection in the nursery and, in turn, transmitted the organisms to its mother[551]

Tetanus This diagnosis merits close attention when the patient who has undergone extensive bowel surgery—especially an abdominoperineal resection—exhibits hyperexcitability and convulsions The author has recovered the *Clostridium tetani* organisms from the posterior wound in such a patient whose convulsions were initially regarded as a manifestation of hypocalcemia or hypokalemia Appropriate prophylactic measures should be instituted when deep lacerations have been sustained in a variety of ways (as, for example from power lawn mower injuries) regardless of how "clean" the wound initially appears Tetanus is a nonimmunizing disease and active immunization is necessary after the patient has recovered The life-saving benefit of a tracheotomy in patients with tetanus merits emphasis[1298] The incidence of tetanus caused by contaminated catgut or surgical instruments has fortunately become very uncommon

Salmonella Enteritis The importance of seeking out this infectious cause of diarrhea following gastric surgery was clearly shown by Waddell and Kunz[595] Many of the cases of this serious complication were initially ascribed to the deranged postoperative physiology, especially if a vagotomy had been performed Another potential cause of nosocomial salmonella gastroenteritis stems from the use of tube-feeding mixtures that contain contaminated commercial yeast[345]

Malaria The recrudescence of a quiescent malaria is occasionally observed following surgical stress and trauma[497]

Tuberculosis The activation or spread of pulmonary tuberculosis following a gastrectomy or the performance of other nonthoracic surgical pro-

cedures was also discussed earlier (p 452) It is further pointed out that hematogenous tuberculosis must be considered in the postpartum patient whose fever and debility cannot be explained [53a]

Dissemination of the Pulmonary Mycoses While the general experience is still rather limited, it appears that both pulmonary blastomycosis and coccidioidomycosis have a tendency to disseminate after thoracic surgery for these lesions [60b] It is possible that prior administration of hydroxystilbamidine may obviate this complication in the former instance Although the problem is not as great with histoplasmosis, care should also be taken before subjecting patients with the more acute forms of this disease to surgery

Meningitis Following Spinal Anesthesia This complication has been reported on a number of occasions, particularly when caused by *Pseudomonas aeruginosa* (p 137) [483 495] It has also followed diagnostic spinal punctures traumatic penetration of the meninges, and pneumoencephalography As noted above one must not overlook a tuberculous meningitis under these circumstances, especially after delivery since the tendency for hematogenous dissemination to occur in the postpartum period is well recognized (p 149) [53a] The low spinal fluid sugar and chloride levels may be most helpful in this regard

Clostridium Welchii Sepsis One should be suspicious of gas gangrene whenever there is an increase in pain about an incompletely débrided and closed wound within the first or second days A similar clue may be the presence of a disproportionate elevation of the pulse associated with increasing weakness listlessness and mental confusion The appearance of the wound the bacterial studies and positive x ray findings confirm this diagnosis

Since *Cl welchii* is a normal inhabitant of the intestinal tract and since fecal contamination of the genital organs not infrequently occurs during or after delivery anaerobic lochial cultures should be taken in patients with unexplained puerperal sepsis When pelvic gas gangrene occurs in the uterus that has been traumatized and contains much devitalized tissue such as dead fetal parts intensive antibiotic therapy and hysterectomy may be in order [1299c] The demonstration of gram positive encapsulated rods in the lochial smears may give the obstetrician an inkling of this infection before the culture reports are returned particularly if the woman also happens to be a diabetic Postabortal *Cl welchii* sepsis might be difficult to diagnose being obscured by both the generalized sepsis the severe hemolytic anemia, and acute renal failure [1 99]

In light of the aforementioned fact that the clostridial organisms are common inhabitants of the human bowel it is not surprising that gas gangrene has followed operations—as well as traumatic wounds—involving the intestines There are instances on record of extensive necrosis of the abdominal wall as a result of this complication [1 99b] It is also recalled that certain gram negative organisms are occasionally capable of producing gas, especially in diabetics

Postsplenectomy Infectious Diathesis A striking incidence of serious infection and sepsis has been observed following splenectomy (p 144) Six of the 19 patients with this complication who were reported by Smith and

his colleagues died[5,2] Such infections are most prone to occur in young children, and usually within two years of the splenectomy The infections that were primarily encountered in this unique group included meningitis (usually due to the pneumococcus), acute benign *pericarditis (particularly* in patients with Cooley's anemia), and acute endocarditis Patients with myeloproliferative diseases who are subjected to a splenectomy constitute another group among which the incidence of serious infection is striking[739]

Other Infections in the Postoperative Period A number of additional important postoperative infections are taken up elsewhere in this chapter These include pneumonitis (p 447), postoperative endocarditis (p 440), ayelonephritis (p 458), pylephlebitis (p 466), subphrenic abscess (p 483), pnd homologous serum hepatitis (p 466)

ENDOCRINE COMPLICATIONS

Pheochromocytoma A significant number of fatalities due to this tumor have been reported not only in association with anesthesia and major surgery, but following incidental procedures (p 22)[68] In their review of the literature, Apgar and Papper found a 50 per cent mortality in patients who were subjected to surgery without prior knowledge of the presence of this disease, death usually being caused by irreversible circulatory collapse[68b] Such complications as a hypertensive crisis during the removal of the tumor and a severe postresectional hypotension must be anticipated In fact, if a significant decrease in blood pressure is not observed following removal of the suspected adrenal tumor, the surgeon would do well to search for an additional functioning adrenal tumor[68c]

A transverse upper abdominal incision should be made if pheochromocytoma is suspected This technique permits access to both adrenals while simultaneously allowing for inspection of the great vessels and the base of the small bowel mesentery for aberrant masses of adrenal tissue[68c]

Adrenocortical Insufficiency This alarming postoperative complication has become more common because of the residual adrenal suppression following previous steroid therapy, sometimes incurred as long as one year previously (p 14)[20] It should be suspected when unexpected collapse occurs following surgery, particularly when significant numbers of eosinophiles *are encountered in the peripheral blood* (instead of the anticipated eosinopenia)[1300] Other causes of acute postoperative adrenal *insufficiency* include trauma to the adrenals, severe sepsis and the usual stress of surgery in the patient with unrecognized chronic Addison's disease Both renal and adrenal cortical failure due to secondary amyloidosis have complicated *the postoperative course of patients with tuberculosis,* chronic ulcerative colitis, rheumatoid arthritis, chronic fistulas, and other chronic pyogenic infections which require surgical intervention[198] Furthermore, patients receiving cortisone or its analogs must be carefully observed for infection and other postoperative complications, the manifestations of which may be suppressed by the steroids[1]

After one adrenal has been resected in a patient with the Cushing syndrome, replacement therapy with cortisone is almost always mandatory, however low the levels necessary[88] The prolonged suppression of the

opposite adrenal becomes manifest by such symptoms as languor, anorexia, nausea, and weakness each time the dose of the hormone is reduced too low On the other hand, a serious metabolic alkalosis can result postoperatively due to the insufficient administration of potassium prior to surgery and the giving of excessive amounts of hormones and salt after the operation

The profound nature of the "compensatory" adrenal atrophy that occurs in the contralateral adrenal because of the severe and prolonged inhibition of endogenous adrenocorticotropin production requires repeated intermittent exogenous ACTH stimulation over long periods Otherwise, hypoadrenalism could rapidly recur [19] In an effort to reactivate the atrophic gland it is suggested that the dose of the cortisone (or the replacement steroid being used) be very gradually tapered off over a period of at least several months (except during periods of stress) During this interval, repeated intermittent courses of ACTH in high dosages are concomitantly administered Although a dose of 25 mg or more of cortisone offers complete replacement therapy of this hormone in most instances such amounts will perpetuate the pituitary depression

Postoperative Diabetes Insipidus This disorder is quite unusual as a postoperative complication Nevertheless it must always be anticipated following intracranial operations in which the hypothalamico-neurohypophyseal system might be injured (p 33) For example instances of this condition have been observed following total hypophysectomy[104b] and the removal of a craniopharyngioma [104] The usual absence of significant hyponatremia in patients who have been subjected to hypophysectomy can be explained by the fact that the adrenal control of sodium metabolism through aldosterone is, to a large extent, independent of the pituitary influence [377b]

Hypothyroidism Spontaneous or drug induced myxedema can seriously complicate the course of surgical patients primarily because of the associated increased sensitivity to drugs and the tendency to laryngeal edema Cardiovascular complications and vascular collapse during anesthesia often develop in patients with either unrecognized or inadequately treated hypothyroidism [1301]

With reference to the unrecognized forms of this disorder, specific mention is again made of (1) the inhibition of thyroid gland function by the prolonged administration of thyroid substance (the Farquharson phenomenon)[36] or iodide [38] and (2) the possibility of symptomatic hypothyroidism in primary pituitary or adrenal disease (p 17) In the case of symptomatic hypothyroidism patients can be precipitated into an acute adrenal crisis by the sole administration of thyroid hormone even when given in small amounts Post thyroidectomy myxedema must always be borne in mind when patients have persistent vague symptoms after this operation [27]

Postoperative Hypoparathyroidism This complication must be anticipated in *all* thyroidectomized patients, particularly in view of the serious acute and chronic sequelae that might eventuate if the condition is left untreated Its manifestations include paresthesias, ocular spasms, mild tetany, mental aberrations, and epileptiform seizures (p 27) [81] Hypopara-

thyroidism should also be anticipated following the removal of a hyperfunctioning parathyroid adenoma In this situation, the remaining parathyroid glands are often left in a temporarily hypoactive state The frequent checking of the urinary calcium by means of the Sulkowitch test might aid in assuring the presence of adequate serum calcium levels, but cannot be relied upon for early detection of vitamin D or dihydrotachysterol overdosage

Ten patients have recently been presented with postoperative and idiopathic hypoparathyroidism (not with pseudohypoparathyroidism) who demonstrated *hypocalcemic hypercalciuria during vitamin D and dihydrotachysterol therapy* [8 b] These agents may directly decrease the tubular reabsorption of calcium thus producing hypercalciuria Positive values for urinary calcium may not, therefore, be indicative of satisfactory serum calcium levels nor may the absence of tetany, inasmuch as many patients with chronic hypoparathyroidism can tolerate low blood calcium levels rather well One should nevertheless attempt to achieve relatively normal blood calcium levels and try to prevent the development of renal calculi by forcing fluids

Development of unexplained tetany or disturbed psychomotor activity following removal of a functioning parathyroid adenoma should suggest *magnesium deficiency* There is a marked drop in the serum level of this element under such circumstances, related to the shift of magnesium into the intracellular compartments [41c] This response is probably exaggerated by extensive bony demineralization preoperatively

Other Complications of Thyroidectomy In the incompletely prepared patient with Grave's disease a fulminating *"thyroid storm"* may be precipitated during or after surgery This state is characterized by fever, heart failure, and even death Fortunately it is rarely encountered nowadays and can be treated more satisfactorily than previously with intravenous hydrocortisone This alarming complication points out the need for a correct clinical evaluation of the therapeutically induced euthyroid state on the basis of the pulse, the gain in weight, the response of the patient s nervousness and sweating and the change in heart size—in addition to the results of metabolism tests

Suspected *damage to the recurrent laryngeal nerves* must be checked by laryngoscopy It is important to appreciate the fact that the voice may be clear following section of *both* recurrent laryngeal nerves, with neither vocal cord abducting In this situation, however severe respiratory obstruction is apt to ensue, particularly with effort After the respiratory obstruction of bilateral cord paralysis is relieved by an immediate tracheotomy, studies should be instituted at once for detecting thyroid or parathyroid deficiencies These complications tend to occur more frequently in the presence of damage to the laryngeal nerves [130]

Malignant exophthalmos may be first observed after medical or surgical control of the hyperthyroidism This presumably results in part from the ensuing overproduction of thyrotropin by the pituitary The oral or intramuscular administration of reserpine might prove to be beneficial in this instance [44]

Persistence of Hyperinsulinism The surgeon who is operating upon

a patient for a presumed pancreatic adenoma that is producing the syndrome of hyperinsulinism has to be aware of the following three considerations (1) *all* the adenomas must be removed (in 18 6 per cent of these lesions in one series, the tumors were multiple),[56] (2) while uncommon, ectopic tumors do occur (as was the case in 3 6 per cent of Howard s series) [49] and (3) prompt examination of the excised specimen by the pathologist is necessary, both to confirm the islet nature of the tumor and to be sure that the lesion was completely removed

The almost universal frequency with which re-exploration has been required in those patients in whom no tumor was originally found and in whom no other cause for the persisting hypoglycemia could be ascertained justifies the performance of a radical operation at the first procedure (p 20) [55] A five year follow up may *not* be long enough to rule out of the possibility of a recurrent or persistent functioning tumor

Parathyroidectomy Failures The surgeon who only occasionally attempts a parathyroidectomy may encounter considerable difficulty in performing a successful operation This is particularly apt to be the case if there are multiple adenomas, if the parathyroid adenoma is embedded in the thyroid, the thymus or elsewhere in the neck or mediastinum and if there are coexisting thyroid adenomas [69c 897d]

COMPLICATIONS OF DRUG THERAPY

Allergic Reactions Serum sickness urticaria, purpuric eruptions drug fever and other reactions may be delayed in their onset for as long as several weeks following surgery (pp 62 and 225)

Excessive or Aberrant Response to Drugs In liver disease, adrenocortical insufficiency and hypothyroidism the dosage of the narcotics and other medications should be considerably reduced Similarly, the use of opiates in emphysema, asthma and primary pulmonary hypertension is frought with danger (p 278) [880] The alert reaction can follow the administration of practically any therapeutic drug and has even been observed with the barbiturates and the tranquilizers (p 392) [1164a]

Hypotensive and Other Cardiovascular Effects of Drug Therapy Profound postural hypotension and circulatory instability may ensue following full atropinization, morphine meperidine and the hypotensive drugs [1303 1305] These sequelae might prove to be disastrous in patients with unrecognized aortic stenosis or coronary insufficiency (p 432) The effects of reserpine can persist for ten days or longer following its cessation particularly in patients who have received long courses of antihypertensive therapy [1303]

These responses are enhanced by the potentially hypotensive anesthetic agents and certain positions most notably the left lateral one Similarly, the influence of both chlorpromazine and promethazine in dampening or abolishing the reflex control of the circulation predisposes to hypotension particularly with changes in the body position on the operating table [1264]

Doses of atropine in the range of 1 mg or excessive amounts of meperidine (with its muscarinic effect) can produce dangerous tachycardias and rhythm disturbances especially in the presence of coronary disease

and in the digitalized cardiac patient [1264a] (Lesser amounts of atropine may be necessary, however, in patients who are prone to cardiac arrest) The dosage of morphine should generally not exceed 10 mg unless it is given in divided doses

Withdrawal Syndrome This disorder might pose a most serious clinical enigma in either chronic alcoholics or narcotic addicts if the patient is unable to give an accurate history It should be emphasized that mild degrees of addiction can develop in surprisingly short periods of time The possibility of a withdrawal reaction should be seriously considered when unexplained personality aberrations occur in physicians, nurses, medical technicians, and other personnel who are allied to the medical profession Meperidine (Demerol) addiction is notorious for its incidence in this regard The same cause should be considered when unaccountable convulsions occur in the early postoperative period

The potentialities of true addiction by the chronic and excessive use of the barbiturates are not fully appreciated [1164d] Similarly, the prolonged use of meprobamate and the other tranquilizers—particularly in individuals who are known to have been addicted to either drugs or alcohol—can also result in addiction (p 392) [1164b, c]

DERANGEMENTS IN NUTRITION, BODY FLUIDS, AND ELECTROLYTES

Postresectional Nutritional Derangements Significant metabolic alterations and fat losses can be expected to occur when less than six feet of mesenteric small bowel remain This is particularly true if the ileum, the ileocecal valve, and the colon were also resected [133b, 1306] The major derangements following extensive bowel surgery consist of steatorrhea, protein loss, hypokalemia, and calcium depletion The profound losses of calcium in the stool that supervene with this type of surgery not uncommonly result in negative calcium balance and actual tetany

Ruffin and his colleagues studied 79 peptic ulcer patients who had been subjected either to a gastrectomy or to a gastroenterostomy combined with a vagotomy at least six months prior to testing for fat absorption with I^{131} labeled fat They found definite evidence of impaired fat absorption in 53 per cent of these cases [16]

Hypoproteinemia and Malnutrition All surgeons should appreciate the serious postoperative complications that may ensue if the patient's preoperative deficient nutritional status is not corrected, at least in part Blood, proteins, calories, and vitamins are all necessary Several weeks are usually required to prepare the depleted elderly individual for elective surgery [1262] It is emphasized that a considerable deficit in the red cell mass can exist even in the face of relatively normal hemoglobin and blood protein concentrations

Serious vitamin deficiency syndromes must be specifically anticipated in both the pre- and postoperative phases when dealing with hyperthyroidism and the other hypermetabolic states Reference was made earlier to the possible induction of a postoperative thiamine deficiency syndrome that may closely simulate thrombophlebitis [139]

Diabetes Mellitus The operative and postoperative difficulties that

can be introduced by this disorder are legion They are specifically related to the predisposition to infection (particularly within the urinary tract), the significant incidence of generalized vascular lesions, the occurrence of abdominal pain in acidosis, and the many problems that are associated with the actual management of this metabolic derangement (pp 71–74) [254] For example, the administration of excessive insulin for the glucosuria that results from an intravenous infusion of glucose postoperatively—in the absence of ketosis—can lead to serious hypoglycemia [1315a] It is pointed out that the rapid infusion of a 10 per cent fructose solution may be attended by abdominal pain of varying severity The exact mechanism of this response has yet to be clarified [287b]

The presence of unusually high or low renal threshold levels in certain diabetics may significantly confuse the postoperative status of these patients Unless the blood levels are frequently checked in such instances the dangers of either uncontrolled diabetes or insulin overdosage exist if the sole guide to regulation is the glucose reduction reaction in the urine

Hypoglycemia This diagnosis must be considered and anticipated in certain patients who demonstrate recurrent seizures and mental aberrations in the postoperative period [43] These individuals include those with adrenocortical insufficiency anterior pituitary hypofunction, severe liver disease, thyrotoxicosis, large abdominal or thoracic tumors and sprue (p 20) An unrecognized pancreatic adenoma in the presence of multiple familial endocrine adenomas may first make its clinical appearance after treatment for or the removal of a parathyroid or pituitary tumor [5] Dangerous hypoglycemia has also ensued following adrenalectomy for a tumor that was producing the Cushing syndrome [89] and in the child delivered of a diabetic mother (as a result of the compensatory changes induced in the islets of the infant's pancreas) [1314]

It is of interest that hypoglycemic manifestations have been observed to follow infusions of dextrose, but not of fructose This presumably represents a reactive phenomenon to the hyperglycemia similar to the situation encountered in postabsorptive hypoglycemia [1315b]

Preoperative Hypovolemia The stress of major surgery can be most hazardous to the patient with unrecognized and untreated hypovolemia This fact has been given increasing recognition by anesthetists Hypovolemia is particularly prone to occur in patients with neoplastic or ulcerative lesions of the large bowel those who have been bed ridden or in body casts for prolonged periods individuals who have undergone multiple operations elderly persons who have led a sedentary existence and in patients who have lost large amounts of fluid

The reasons for such concern are best understood by an enumeration of the following hazards that might be encountered in the anesthetized hypovolemic patient diminished circulatory reserve inability to compensate for the depressant effects of the anesthetic agents or their adjuncts, intolerance to changes in body position inability to compensate for major hemorrhage and the profound hypotension produced by relatively minor degrees of blood loss [1264]

Iatrogenic Heat Stroke The breakdown of the heat regulating mechanism—as characterized by the cessation of sweating and subsequent hyper-

pyrexia—must be guarded against during protracted heat spells with excessively high night temperatures This is particularly true in the case of elderly or cardiac patients, and in wards or operating rooms that are not air conditioned or adequately ventilated (p 106)

Heat stroke can be precipitated by a number of other factors in preparing patients for surgery These include the use of atropine, the prolonged restriction of food and liquids, the close proximity of lighting systems to the patient, the retention of heat by inspiration of anesthetic atmospheres, and the use of gowns and drapes which interfere with or reduce convection and evaporation [378] Both hyperthermia and hypoxia must be carefully avoided in infants and children, in particular, under these circumstances [1312b]

Dehydration and Fever It has been shown that the combination of fever, dehydration, general anesthesia, and carbon dioxide accumulation predisposes to convulsions This is most frequently observed in the febrile, dehydrated child with acute appendicitis who is unnecessarily subjected to emergency surgery without adequate preoperative hydration [1308]

Dehydration Resulting from Prolonged Nasogastric Tube Feeding Due to the excessive protein intake and the concomitantly induced dehydration, a severe hypernatremia hyperchloremia, and azotemia may complicate this form of alimentation [308] A negative water balance with subsequent dehydration and a decreased extracellular volume precede the extracellular hyperosmolarity induced by high protein nasogastric tube feeding This problem is most apt to be encountered when patients have impaired thirst mechanisms, as might occur in obstructive esophageal disease or with impaired consciousness [308b]

Hypodermoclysis Induced Complications The administration of an electrolyte-free isotonic solution or any hypertonic solution by the subcutaneous route can induce hypotension, oliguria, and peripheral vascular collapse due to the sudden fluid shifts that may be so induced [1313] This method should be employed only after pre existing fluid and electrolyte deficits have been corrected particularly in elderly and debilitated patients Dextrose solution given by clysis could also intensify an existing salt deficit

General Comments Relating to Specific Postoperative Electrolyte Derangements It is obviously impossible to enter into a full discussion of the many problems pertaining to the postoperative administration of fluids and electrolytes in this section A few complications will be set forth that are not generally recognized, the awareness of which might be of vital importance to the safe conduct of surgical patients both during and after operation The surgeon must be cautioned however to avoid the ever increasing tendency of employing clinical chemistry as a "wastebasket" It has become fashionable to attribute various postoperative complications, such as adynamic ileus and mental confusion, to slight aberrations in the concentration of the serum electrolytes

HYPONATREMIA The complication of salt depletion in the postoperative state is alluded to many times in this section One must obviously supplement the losses of sodium chloride that occur by way of the urine the perspiration, vomitus draining fistulae and intestinal and gastric suction Hyponatremia poses a particularly threatening complication in the

postoperative course of infants and children Under these circumstances, it is often encountered in association with water intoxication or hyperpotassemia [1312a]

On the other hand the practice of giving *no* salt at all postoperatively has gradually grown in many hospitals Some sodium chloride is obviously necessary to replace the minimal losses incurred during the first five days postoperatively in order to obviate the serious hypotensive and other cardiovascular sequelae of salt depletion This deficit usually amounts to 200 or 300 mEq , and can be readily replaced by the administration of approximately 300 ml of an isotonic saline solution daily after the first two days postoperatively

It is not generally appreciated that sodium deficiency is often manifested by hypovolemia rather than by hyponatremia Paradoxically there are many patients who are seriously ill from a variety of causes in whom an unexplained severe hyponatremia develops which bears no overt relationship to salt loss and for which saline administration might actually be detrimental (p 247) [304]

HYPOKALEMIA In the patient with gastrointestinal obstruction and in the patient who is subjected to constant gastric suction without the large losses of potassium being anticipated and replaced severe ileus lethargy weakness and an associated hypochloremic alkalosis often ensue (p 79) [291, 297] It is particularly important to differentiate this complication from "surgical ileus Delirium, tetany and electrocardiographic abnormalities can also occur

In patients who are on the verge of clinical digitalis toxicity the reduction in the blood potassium by oral or intravenous carbohydrate has precipitated various ventricular arrhythmias [300] This suggests that patients receiving large doses of digitalis (and who have well functioning kidneys) should be placed on a high protein and low carbohydrate diet supplemented by potassium salts

MAGNESIUM DEFICIENCY Prolonged parenteral fluid administration in the presence of chronic alcoholism or diarrhea is most apt to induce this disorder Clinical magnesium deficiency is characterized by tremors choreiform movements convulsions delirium and coma [41] Its occurrence after parathyroid surgery was alluded to above (p 172)

Excessive Diuresis In addition to inducing hyponatremic hypokalemic and dehydrated states and potentiating the serious effects of both digitalis intoxication and water intoxication (*vide infra*) other undesirable sequelae are apt to result from an excessively rapid and intense diuresis These include the precipitation of gout tetany phlebothrombosis thromboembolism and cerebral thrombosis (p 211) [270d, 772, 773, 811f] The renal tract complications were discussed earlier (p 460) Marked degrees of salt and water depletion have also been encountered in patients with prolonged prostatic obstruction following decompression of the bladder [192, 193]

Overhydration The excessive infusion of nonelectrolytic solutions (principally dextrose in water) may result in *the syndrome of water intoxication* The features of this condition closely resemble the symptoms of increased intracranial pressure—namely nausea vomiting bradycardia dimness of vision muscular twitching disorientation convulsions and

coma[1309] This state can be rather readily induced when the blood pressure and renal blood flow are reduced, or when there has been an unsuspected preoperative depletion of sodium

Water intoxication of serious proportions has also followed the use of "simple tap water enemas" or barium enemas This complication is particularly prone to occur in infants, in whom half the extracellular fluid is represented by the daily water intake and output (in contrast to a corresponding proportion of only one-seventh in adults)[1310]

Water intoxication may also occur from the absorption of large quantities of the irrigating solution that are used under a high head of pressure during a transurethral electroresection of the prostate gland During or shortly after the procedure, the patient may suddenly exhibit restlessness, nausea, dyspnea, cyanosis, and hypertension A fall in the serum sodium was found in 14 of 15 such patients studied in one series[1309c] This particular complication may be averted to a large degree by reducing the irrigating pressure

Hyperchloremic Acidosis and Hypokalemia Following Ureterosigmoidostomy This complication results from the excessive reabsorption of chloride from the rectal mucosa Fortunately, it can be readily treated once recognized[307] Stamey has stressed the profound and insidious potassium deficiency that may also be created by ureterosigmoidostomy[1311a] In addition, there may be an associated normochromic anemia and significant disturbances in the carbohydrate metabolism[1311b]

It is of interest that ammoniagenic coma is encountered as a sequel of ureteroenterostomies in man only when the liver function becomes impaired In this situation the increased load of ammonia in the portal circulation becomes manifest by a rise in the peripheral blood ammonia level[1311c]

Excessive Salt Administration The majority of postoperative patients do *not* require saline infusions the first one or two days Postoperative sodium intolerance due to the decreased renal excretion of sodium may result from the increased secretion of aldosterone created by either relative sodium depletion or the excessive intake of water[1307] It is wise to avoid surgery in women with cardiac disease prior to and during their menstrual periods because of the well known retention of water and sodium that takes place at these times[1212b]

A severe *chloride acidosis* might be induced by the intravenous infusion of excessive quantities of isotonic saline (i e, the routine use of a liter or more of saline) It is recalled that the normal concentration of the extracellular fluid chloride approximates 100 mEq /L, whereas that of isotonic sodium chloride is 150 mEq /L This is a particularly dangerous situation in the older age groups especially when marked depletion of the potassium stores has already occurred

Ammonium Intoxication Following Portacaval Shunts See "Hepatic Complications" (p 466)

Hypernatremia and Hyperchloremia Following Surgery in the Region of the Hypothalamus and Third Ventricle See Group II (p 82)[309]

NEUROLOGIC COMPLICATIONS

Cerebrovascular Accidents. These sequelae of surgery have not received their deserved emphasis.[126] The occurrence of sudden personality changes, anorexia, and unexplained vague symptoms in the hypertensive or arteriosclerotic patient postoperatively strongly suggests that a "small stroke" has taken place, affecting one of the "silent areas" of the brain. This is most apt to ensue following prolonged periods of hypoxia or hypotension, especially with spinal anesthesia.[1090] Since acute cerebral vascular occlusion *per se* may be the cause of hypotension and T wave inversion, it might readily be mistaken for coronary occlusion in the postoperative period.

Anesthetists should appreciate the fact that dilatation of the pupil occurs promptly when either the circulation or the oxygenation of the brain becomes inadequate. There is still much to be desired, however, concerning the presently available monitoring systems for the detection of cerebral hypoxia on the operating table. It is quite possible that the small electroencephalographic units which have been developed for use during open heart surgery will also be ultimately utilized during other procedures (p. 443).[1, 871]

Cerebral embolization is a constant concern in patients undergoing operations on either the mitral or aortic valves when clotted atria and calcified valves are encountered. This is particularly true in patients over the age of thirty five and in the presence of auricular fibrillation. In view of the high frequency of thrombosis to the left auricular appendage (present in about one third of patients with mitral stenosis) the risk of embolization when the appendage of the left atrium is used as the site of entry for mitral surgery is at once apparent.[865b] Temporary interruption of the cerebral circulation, along with vigorous flushing of the atrium before insertion of the finger has been carried out by certain cardiac surgeons with some measure of success in preventing this complication.[1317]

The timing of a mitral valvuloplasty in relation to previous peripheral embolization is usually arbitrary, but poses a relatively frequent consideration (having occurred in 19 per cent of 1000 patients who were subjected to this procedure).[856d] In general it would appear wise to institute anticoagulant therapy for three to four weeks before operating.

Ischemia of the Spinal Cord. Attention is briefly directed to another potentially serious central nervous system complication stemming from surgery upon the aorta, namely, ischemia of the spinal cord.[1316a] The anatomic and physiologic background for such an ischemic process is complex by virtue of the many structural and dynamic variables in the circulation that are involved. It will be recalled that the entire spinal cord (except for part of the cervical cord), the nerve roots, the dorsal ganglia and the peripheral nerves are perfused by the aorta distal to the left carotid artery. Consequently, a suprarenal occlusion of the aorta for any appreciable period during thoracic surgery—in the course of which the vital collateral circulation distal to the stenosis of the aorta might be compromised by ligature of the lower thoracic intercostal vessels—could result in a permanent and crippling deformity. The seriousness of this complication could

be well out of proportion to the magnitude of the original disorder. This is an especially valid consideration in the surgical correction of coarctation of the aorta.

The disadvantages of general body hypothermia and temporary artificial shunts that were previously used in an attempt to protect the spinal cord have apparently been overcome by the development and perfection of controlled extracorporeal circulation with aortic by pass techniques. This has permitted the successful resection of virtually the entire descending aorta without significant neurologic sequelae, even when attended by periods of aortic occlusion exceeding one hour.[1116b]

Neurologic Complications Following Spinal Anesthesia. On infrequent occasions, radiculitis, the cauda equina syndrome, ascending myelitis, adhesive arachnoiditis, meningoencephalitis, and a bacterial meningitis have followed spinal anesthesia (p. 379).[483, 485, 1131, 113] Spinal anesthesia may also clinically *precipitate certain pre-existing neurologic disorders*—most notably multiple sclerosis, combined system disease, diabetic neuropathy, spinal cord tumor, and the other "degenerative" diseases of the cord.[1133]

Repeatedly unsuccessful attempts at lumbar puncture suggest that an obliteration of the subarachnoid space exists. There is still considerable controversy as to whether the meningeal changes in the nonbacterial complications represent a hypersensitivity to the anesthetic agent, or a direct toxic effect. The latter may stem from either the drug itself or the detergent solution in which the ampoules are kept. (Also see Infectious Complications, p. 169.)

Puerperal Hemiplegia. This disorder is characterized by headache, generalized or focal seizures, and focal paralysis. It appears several hours to several weeks after delivery. Although it is usually due to a thrombosis of the superior longitudinal sinus, most patients will recover without the use of anticoagulants.[1038] Aphasia, coma, mental symptoms, blindness, and a fluctuating hypertension may also be present. If the latter occurs, this condition can be readily confused with postpartum eclampsia.

Postpartum Pre-eclampsia. Inasmuch as it is not uncommon for pre-eclampsia (or even eclampsia) to take place during labor or within the first two days post partum, the use of potent vasoconstrictive drugs should be avoided in patients who are particularly vulnerable to the sequelae of further physiologic vasoconstriction in the kidney, the placenta, the heart and the brain.[888a] Mention is again made of the current feeling that pre-eclampsia may actually represent the first evidence of an underlying hypertensive diathesis, notwithstanding the subsequent normalization of the blood pressure in the puerperium.

Precipitation of a Myasthenic Crisis. A crisis might be precipitated in the patient with unsuspected myasthenia gravis by the administration of a curare-like drug for anesthetic purposes. Should such a situation be suspected, it is apparent that an adequate airway must first be established and that secretions be promptly cleared, even if a tracheotomy and a respirator are necessary. If one can be sure that the patient has not taken any previous medication for this myopathy—which would exclude the possibility of a "cholinergic" crisis due to an overdosage with the cholinergic agents—it is best to give Tensilon in a dose of 2 mg intravenously. The

needle should be left in place and the response noted Prompt improvement is indicative of a myasthenic crisis and warrants further therapy with the cholinergic drugs However should there be no effect (even after an additional 8 mg are given) and muscle fasciculations appear, a cholinergic crisis must be suspected In this situation, intravenous atropine (in the dose of 1 3 mg) is in order (Also see p 371)

The surgeon who resects a thymoma should be aware of the fact that myasthenia gravis has been known to make its initial clinical appearance following this type of procedure [1118g]

Considerations Relating to the Delivery of the Pregnant Myasthenic Patient If adequate cholinergic therapy is taken by the pregnant myasthenic patient, labor and delivery will usually proceed normally The decision to perform a cesarian section should be dictated *solely* by obstetric indications [1118f] In 16 live births from a series of 22 myasthenic mothers reviewed by Osserman, there were three cases of acquired neonatal myasthenia gravis the symptoms of which usually abated within the first few weeks of life During this period, cholinergic therapy may be required [1118e]

Hypersensitive Carotid Sinus and Complications of Surgery for Carotid Body Tumors The possible hypersensitivity of the carotid sinus mechanism must be borne in mind when cardiac or cerebral symptoms are related to changes in the position of the head neck, and body, or to pressure on the neck structures (p 293) [859, 893]

There may be dire complications stemming from the casual performance of surgery on unrecognized carotid body tumors This is especially apt to be the case if it is done under local anesthesia and with inadequate exposure [897b] Every effort should be made to avoid injury to or sacrifice of the carotid artery by a careful dissection in the serosal layers of these vessels Encouraging results have been reported with the use of carotid artery homografts The profound sequelae of ligation of the common or internal carotid arteries is pointed out by the mortality rate of 30 per cent in a series of 88 consecutive carotid ligations reported by Moore and Baker, with serious neurologic complications and hypotension occurring in almost one half of the survivors [897] Resection of some of the adjacent nerves (viz the vagus the hypoglossal, the spinal accessory nerve, or the sympathetic chain) can result in palatal and vocal cord paralysis paralysis of the tongue weakness of the shoulder girdle and a Horner s syndrome, respectively

Partial Facial Nerve Paralysis This has followed general anesthesia It is usually the result of the application of strong pressure to the lower jaw in an attempt to maintain an open airway [1318a]

There are many social and economic problems attendant upon a partial or complete paralysis of the facial nerve following parotid gland surgery for either benign or malignant neoplasms Much of this disability can be corrected by restoring the anatomical continuity of the facial nerve either during the initial procedure or as soon thereafter as is feasible [1318b] The regeneration of the nerve that follows such a procedure—even if a graft of the facial nerve is necessary—will frequently re-innervate the affected muscles

The Auriculotemporal Syndrome This interesting disorder occurs as

a late sequel to injury in which the auriculotemporal nerve is traumatized This injury is usually the result of either a postoperative parotitis and abscess, the excision of a parotid tumor, or the resection of the descending ramus of the mandible [13180] A sufficiently long interval to allow for the regeneration of the damaged nerve is required, however

The clinical episodes are provoked by a salivary stimulus They consist of flushing and sweating over that area of the skin that is supplied by this particular nerve Such gustatory sweating can be attributed to many pathophysiologic mechanisms Of those that have been set forth, the misdirected re innervation of the sweat glands by parasympathetic fibers in association with a supersensitivity to acetylcholine appears to be the most plausible (The sweat glands normally have a predominant sympathetic innervation)

Should the discomfort prove to be very annoying, relief can be permanently achieved by the intracranial division of the glossopharyngeal nerve It is of interest that patients who have undergone bilateral cervical sympathectomies with the removal of the superior cervical ganglion on one side do not experience gustatory sweating, or even sweating of the face during hot weather

Sequelae to the Removal of a Subdural Hematoma The following potential complications that may ensue after the removal of a subdural hematoma are not generally appreciated [1114b] First, a sudden expansion of the brain subsequent to the release of the pressure can induce severe cerebral edema this, in turn, may increase the neurologic deficit Lumbar puncture and dehydrating regimens have usually proved efficacious in such a situation Secondly, the relaxation of the dura after this particular procedure could cause it to separate from the bone This might be followed by an extradural hematoma which would also require evacuation Thirdly, the retention of part of the membrane within the cranium due to the surgeon's inability to completely detach this structure from the arachnoid is known to be the basis for the failure of the brain to expand The space so created tends to become filled with cerebrospinal fluid, which thereafter might produce various neurologic signs and symptoms (especially in the older age groups) Finally, the incidence of epilepsy following evacuation of the hematoma is generally set at 25 per cent

Fat Embolism See "Vascular Complications" (p 444)

Water Intoxication See "Derangements in Nutrition, Body Fluids, and Electrolytes' (p 477)

COMPLICATIONS OF RADIATION

Because of the long latent periods involved, many sequelae of postoperative radiation injury are often attributed to the surgery itself or to metastases and other complications of the original disease Although the designation "postoperative" may not be completely accurate, the inclusion of these complications is nevertheless pertinent Among the more common are the following

Radiation pneumonitis following therapy for mammary, lung, mediastinal, or esophageal carcinoma and lymphoma (p 398) [1199 L00]

Radiation pericarditis following radiation for lesions of the breast or chest (p 400)

Radiation nephritis following therapy directed to the retroperitoneal nodes (p 399)[1201]

Radiation enterocolitis following intensive therapy directed to the pelvis, abdomen, or the retroperitoneal tissues (p 399)[1202]

Radiation proctitis following x ray therapy for carcinoma of the cervix (p 399)[1357]

Radiation esophagitis following irradiation therapy for intrathoracic malignancy in which the maximum dose of 6000 r is exceeded particularly with the increasing clinical use of the betatron and cobalt units (p 399)[1203]

Radiation myelitis following radiation to all parts of the spinal cord included within the therapeutic field (p 400)[1204]

Osseous reactions and *hematopoietic derangements* due to both external radiation and the effects of alpha radiation from radium therapy (p 400)[1205]

These complications have been discussed in Group XIII

COMPLICATIONS OF ABDOMINAL SURGERY

Subphrenic Abscess This complication commonly gives rise to unexplained fever It may be particularly difficult to define when the process occurs on the left side[385] About one third of the patients who develop a subphrenic abscess postoperatively required closure of a perforated duodenal ulcer If one includes the instances in which a duodenal ulcer had probably leaked, the incidence approaches 50 per cent (p 108)[385b]

Since the antibiotics often delay the recognition of postoperative intra abdominal infection, the old dictum of Dennis "Pus somewhere, pus nowhere, equals pus under the diaphragm " merits repetition When the patient cannot take an adequate deep breath and a subphrenic abscess is suspected either observation of the diaphragmatic contraction following external phrenic nerve stimulation or suction tip reconnaissance close against the parietal peritoneum under local anesthesia and drainage might prove to be rewarding (p 828)[1319]

Postoperative Pneumoperitoneum While it is generally held that post operative pneumoperitoneum usually undergoes complete absorption within a maximum period of fourteen days its incidence and duration prior to that time may be extremely variable It has been pointed out that if free air is observed after the first three days in association with definite signs of peritoneal irritation the possibilities of a ruptured hollow viscus or an intra abdominal abscess must be seriously entertained[1319b]

Complications of Counterincision in the Diaphragm for the Repair of a Hiatal Hernia The relative ease of exposure and the reduced incidence of recurrence of hiatal hernias usually favor the transthoracic approach for the repair of this disorder In many areas a counterincision in the dome of the diaphragm is being performed for the following reasons (1) to maintain the reduction of the viscera during the repair, with the cardia being kept in its normal anatomic position (2) to enable the surgeon to fix the

phrenoesophageal ligament to the under aspect of the diaphragm, and (3) to permit exploration of the abdomen

The major hazard to such a procedure is the ability of either the stomach, the small bowel, the colon, or any combination of these organs to herniate through this counterincision [13,0] The use of the thoracoabdominal exposure in certain of these hiatal hernias can obviate such difficulties In view of the potential fatal outcome following a dehiscence in the diaphragmatic counterincision, it has also been recommended that the method of choice in closing such diaphragmatic incisions be imbrication with mattress sutures [13,0b]

Extraperitoneal Pelvic Abscess Inflammation of the prevesical space *of Retzius and the surrounding structures has resulted from prostatic* abscesses, prolonged indwelling catheters, urinary extravasation, diverticulitis of the urinary bladder, and other local pathologic conditions [869]

Actinomycosis One should consider the possibility of actinomycosis in the presence of persistent intra-abdominal sepsis following the rupture of a gastric or duodenal ulcer, rupture of the appendix, rupture of colonic diverticula, or the perforation of a rectal abscess (p 168) [614]

Excessive or Unnecessary Postoperative Procedures Following Bowel Surgery The routine use of constant gastroduodenal suction after every abdominal operation, including cholecystectomy and intestinal anastomosis, is not only unnecessary but potentially detrimental Similarly, routine postoperative orders for neostigmine, vasopressin (Pitressin), cathartics and enemas can be grossly abused [13,18] ' When a person with no nutritional deficit has had a subtotal gastrectomy performed, convalescence is best accomplished by bearing in mind the fact that the human being is well adapted to survival from a single trauma, provided that the normal train *of adaptive responses is not upset by meddlesome therapy To crowd such* a patient with mixed electrolyte solutions, protein hydrolysate, concentrated albumin and jejunostomy feeding is to deny the success of an evolutionary process which has produced an organism quite able to survive a single massive trauma with short term interruption of oral intake "[1321b]

Postoperative Pancreatitis This serious and highly lethal complication occurs more commonly than is generally realized [13] The pancreas is particularly vulnerable to injury during the performance of a total gastrectomy with splenectomy resulting in both pancreatitis and pancreatic fistulae It may also follow many other types of abdominal surgery in which *the pancreas is neither directly traumatized nor mobilized* In a review of nine cases of fatal postoperative pancreatitis at the Mayo Clinic, the lack of a common anatomic pathologic factor and the fact that the operations were often far removed from the pancreas indicated the possibility of humoral borne proteolytic enzymes or even allergic phenomena in the pathogenesis of this condition [13,b]

In the absence of an autopsy, the condition is commonly regarded as "postoperative peritonitis" The use of the adrenocortical steroids in the management of postoperative pancreatitis may be attempted, but only after consideration has been given to the potential pancreatic damage that these agents in *themselves can produce (p 15)* [1186]

Acute pancreatitis often leads to renal failure This may be partly

due to fat embolism resulting from the induced fat necrosis[794] It is also recalled that acute pancreatitis has followed the removal of a parathyroid adenoma on a number of occasions (p 24)[69, 73]

Inadvertent Gastroileostomy Profound weight loss and debility occasionally result from this technical complication[133] The clinical picture and diagnostic considerations of this entity were considered in an earlier chapter (p 41)

The Postcholecystectomy Syndromes This designation has frequently served as an all inclusive wastebasket Such usage is most frequently encountered when the cholecystectomy was performed either for underlying functional complaints without a positive surgical indication, or for unrecognized disease (particularly pancreatitis) The presence of residual stones or strictures may now be accurately determined radiographically with Cholografin or its counterparts (p 762) Other causes for persistent postcholecystectomy discomfort may include a small intraluminal carcinoma in one of the proximal hepatic ducts that was overlooked (p 89), spasm of the sphincter of Oddi and a postoperative neuroma The latter is more apt to follow a mass ligature of the cystic duct and artery, since many autonomic nerve fibers are included in such a procedure

The *cystic duct remnant syndrome* must also be kept in mind One should not jump to the conclusion that a roentgenographically demonstrable cystic duct remnant is the sole cause of a postcholecystectomy syndrome, however, because the incidence of this finding has been found to be as much as two times as great in asymptomatic control patients[329, 1323]

Choleretic drugs can actually aggravate the discomfort of the patient who has undergone a cholecystectomy and accordingly should not be forced If no residual organic disease is likely the patient needs to be reassured with the explanation that the discomfort largely results from the temporary need for elevated intrabiliary pressure to propel the bile following removal of one s gallbladder

Other Complications of Cholecystectomy There are a number of possible complications that may be produced by the rather formidable procedure of cholecystectomy in addition to the above mentioned postcholecystectomy syndromes[13, 36] *Bleeding from the cystic artery* may occur postoperatively either as a result of the ligature coming off or from an accessory cystic artery which was not ligated at the time of surgery (Double cystic arteries can be found in up to one out of four individuals) The presence of *an aberrant origin of the hepatic artery* in over 30 per cent of the population and the numerous *variations of the cystic artery* could worry the inexperienced surgeon Fortunately *infarction of the liver* is rather infrequent by virtue of the usually adequate hepatic collateral circulation, especially if the ligation of the hepatic artery occurred close to its origin from the aorta Infarction of the liver is characterized by right upper quadrant pain and tenderness fever vomiting leukocytosis, jaundice and hemorrhagic complications from the induced hypoprothrombinemia Abscess formation may subsequently further complicate the picture

An *occlusion of the portal vein* in the absence of mesenteric vein or splenic vein thromboses is not usually associated with an alarming clinical picture The postoperative jaundice stemming from the *ligation of the com-*

mon bile duct or of one or both of the major hepatic ducts usually offers little difficulty in diagnosis. On the other hand, an injury to one of the hepatic ducts that is followed by the formation of a loculated bile peritonitis and *ascites with clear fluid could prove to be a difficult diagnostic problem*.[13 3b]

Complications of Operative Bile Duct Injuries. The vast majority of iatrogenic ductal injuries occur as the result of cholecystectomy. To avert complications, they merit early repair by surgeons who are especially competent in this type of plastic surgery. The reader should refer to Norcross and Dadey[13 2d] who have written an excellent summary of a number of these medical complications in their review of 400 unselected cases of bile duct injury studied at the Lahey Clinic.

A decision to explore the common bile duct must be made by the individual surgeon, based either upon the preoperative course or the findings at laparotomy. However, it is well to point out the relatively high percentage of patients undergoing a cholecystectomy who are also being subjected to a choledochostomy (42 per cent at the Massachusetts General Hospital) and the threefold increase in mortality associated with this additional procedure in a survey of over 2200 cholecystectomies at this same institution.[13 e] *Acute pancreatitis is a serious complication when it* occurs following surgical manipulation of the common bile duct.[13 c]

Bartlett and Waddell assessed the reliability of certain indications for choledochostomy in 1000 patients operated upon at the Massachusetts *General Hospital*.[13 2f] *They considered the following as positive*: jaundice, a "palpable stone", and dilatation of the duct system (i.e., a duct wall with an outside diameter of greater than 1 cm., or a cystic duct whose outside diameter exceeded 4 mm.). They observed that the yield of common *duct stones is relatively low when the only indication for exploration is the* presence of small stones in the gallbladder (i.e., less than 0.5 cm. in diameter), and that in this instance the frequency of choledochostomy might be reduced. Even though only a few common duct stones can be anticipated in patients with previous attacks of pancreatitis, *this is another valid* indication for exploration of the common bile duct.

The Postgastrectomy Syndromes. An attempt should be made to differentiate the several postgastrectomy syndromes in order to *allow for a* rational approach to therapy.

1. The most commonly encountered form of the *"dumping syndrome"* is characterized by postprandial weakness, sweating, pallor, tachycardia, nausea, vomiting, diarrhea, dizziness, and other *vasomotor features. These* phenomena result from both the rapid distention of the jejunum,[13 4a] and the rapid passage of the undiluted and hypertonic nutrients in the stomach to the jejunum. There then ensues a sudden dilution of the intraluminal contents by the intravascular and interstitial *crystalloids creating an acute* reduction in the circulating blood volume,[13 4b] intestinal hypermotility, and possibly alterations in the concentration of serum potassium.

2. Another syndrome, closely resembling the aforementioned symptoms but occurring in the late postprandial period (i.e., *two to four hours* after eating), is attributable to a *rebound hypoglycemia*. Both of these clinical pictures respond to a high protein, low carbohydrate diet, small

meals, in between meal liquids lying down immediately after eating, and the use of various antispasmodic drugs

3 Symptoms may be due to the presence of *a small stomach remnant* which produces early satiety and nausea

4 With the gastrectomy induced *digestive and absorptive disturbances*, there may be weight loss steatorrhea creatorrhea avitaminoses, pernicious anemia like changes and iron deficiency anemias

5 Another syndrome is due to *chronic obstruction of the afferent loop*, stemming from adhesions volvulus, or herniation under the efferent loop This is characterized by postprandial nausea and vomiting, with the vomitus containing large quantities of bile stained fluid but no food When vomiting occurs, the symptoms are relieved [13 4, 1377d] This situation can be suspected by the inability to fill the afferent loop with barium It is verified by the absence of bile from the aspirated jejunal contents during the symptomatic period and the appearance of bile with the relief of symptoms Surgical relief of the obstruction is necessary

6 One may also encounter *obstructions involving the efferent loop* In such an instance, the vomitus contains recently ingested food The appearance by x ray usually establishes the diagnosis of this disorder Surgical intervention is likewise indicated here

As was indicated previously one must not attribute an inordinate loss of weight following gastrectomy too hastily to this procedure without first ruling out possible activation of pulmonary tuberculosis and other causes (p 452) [1 76]

Several other unusual complications that have been observed following gastric resection will be briefly mentioned [1324d] *Necrosis or volvulus of the transverse colon* may follow removal of the gastrocolic omentum if the colon is redundant or has a long mesentery *Volvulus of the cecum* is reported as an unusual complication following abdominal surgery [13 6c] *Injury of the common or pancreatic ducts* can occur especially when the resection was performed for an acute posterior penetrating duodenal ulcer Such damage could result in either obstructive jaundice or acute pancreatitis

Acute Dilatation of the Stomach This disorder has proved to be an alarming complication on several occasions in the author s experience It can simulate many acute surgical emergencies in the abdomen particularly the perforation of a peptic ulcer The clinical picture is characterized by a shock like state with tachycardia dyspnea sweating pallor, and abdominal fullness The insertion of a Levin tube is of both diagnostic and therapeutic value

Acute gastric dilatation is also apt to complicate the course of malnourished patients with chronic diseases overwhelming toxemia, overdosage with either the anticholinergic or curare-like drugs intranasal oxygen administered under positive pressure and embolism or thrombosis of the mesenteric vessels It is also likely when brain surgery has been performed or a body cast applied The shock induced by this complication is caused by the tremendous quantities of fluid and electrolytes that are poured into the upper gastrointestinal tract, as well as the mechanical effects of the distention (viz , elevation of the diaphragm compression of the lungs and rotation of the heart on its transverse axis)

Problems Related to Surgery in Regional Ileitis In our present state of incomplete knowledge concerning the nature of this disorder, surgery should be generally deferred in active cases with extensive "skip lesions" Such efforts are best primarily directed to the chronic disease wherein localization and obstructive features are prominent When a complete diversion of the fecal stream is performed by an ileotransverse colostomy, the unaffected area of the ileum proximal to the diseased area must be divided Otherwise, one may have to cope with a large dilatation of this small bowel segment at a later time, with the attendant diarrhea, fever and other evidences of the activated disease

Even the most experienced of surgeons with a particular interest in this disease have been fooled by an acute ileitis masquerading as appendicitis, as well as a host of other conditions (p 49) In such an instance the bowel and appendix should be *left alone* and the abdomen *promptly closed* since (1) the appendix is rarely involved, and (2) 65 per cent of these cases will remit spontaneously[167] Where there are segments of jejunal involvement, localized resections are preferred to the short circuiting operations

Bowel Impaction It must be appreciated that this embarrassing (and serious) complication is particularly prone to occur postoperatively in elderly patients with the chronic laxative habit The impaction is not always confined to the rectum Barium taken by mouth might also become inspissated, contributing to the ileus Other pre- and postoperative causes of bowel obstruction are considered in the next chapter

Complications Resulting from Gastrointestinal Intubation Chaffee has cited the following accidents that have resulted from the use of Levin and Miller Abbott tubes sinusitis and otitis media, esophageal stricture laryngeal obstruction knotting of the tube rupture of an esophageal varix rupture of various organs, including the esophagus, the stomach, and the small bowel, inability to withdraw the balloon tipped tube, and breakage of the mercury-filled bag[13 6] Should the mercury bag pass the ileocecal valve, it must not be withdrawn, but should be permitted to pass spontaneously by the anus Swallowing of the Miller Abbott tube is infrequent, but has occurred[1326b]

Extrauterine Complications of Pregnancy Abdominal complications in pregnant women that necessitate surgery are fortunately infrequent, having been encountered in 41 patients among a total of 45,720 deliveries over a five year period at two institutions[1325] They are nevertheless important to consider because of the following factors (1) maternal death may result if they remain untreated (2) the differential diagnosis between these disorders and the various complications related to the pregnancy itself (viz degeneration or torsion of a uterine myoma, ectopic pregnancy induced abortion, abruptio placentae toxemia) or renal colic may be very difficult, and (3) abortion is more apt to occur from the procrastination of surgery than from the prompt performance of the indicated procedure

Appendicitis may occur during *any* phase of pregnancy and merits consideration in the presence of persistent abdominal pain, nausea, and vomiting It was definitely present in 22 patients in the series cited above Other conditions that might be encountered include a Meckel s diver

ticulitis, torsion of an ovarian cyst or a fallopian tube, volvulus of the intestine (p 506), ileus and intestinal obstruction (p 505), an acute cholecystitis (very uncommon), and rupture of a splenic artery aneurysm (p 299)

Barter and Rovner also make mention of the following two infrequently considered obstetric complications which could simulate an acute abdominal crisis (1) the round ligament syndrome caused by the stretching of this structure, especially when on the right side (the finding of tenderness on direct palpation of the ligament might avert a needless appendectomy) and (2) gestation in an anomalous uterus, with pain being produced by the inequality of the uterine enlargement especially during the middle trimester [13, 5]

GROUP XVI

Medical-Surgical Diagnostic Problems Relating to Obscure Abdominal Pain, Gastrointestinal Hemorrhage, and Intestinal Obstruction

EXTRA-ABDOMINAL CAUSES OF ABDOMINAL PAIN

Constitutional Disorders

Infections

Neurologic States

Affections of the Parietes

Urologic Problems

Intrathoracic Conditions

MASSIVE GASTROINTESTINAL HEMORRHAGE OF OBSCURE CAUSE

Gastritis Postbulbar ulcers Lesions of the small bowel Nonspecific ulceration at the ileocecal area Uremia Poisonings (arsenic and mercury) Hiatal hernia The Mallory Weiss syndrome Peptic ulcer of the esophagus Symptomatic bowel bleeding during anticoagulant therapy Diverticulitis Ischemic infarction of the liver Retroperitoneal hemorrhage Rupture of a saccular arteriosclerotic aneurysm Hemorrhagic telangiectasia and angiomas of the bowel Meckel's diverticulitis Jejunal diverticuli Henoch's purpura Choledochal hemorrhage Pancreatic cancer Esophageal varices Portal hypertension Salicylate ingestion Reserpine therapy Other drug induced ulcerations Tuberculous adenopathy Extensive amyloidosis Elastica disease Ruptured corpus luteum Radiation proctitis Hyperparathyroidism Alpha or beta cell tumors of the pancreas Curling's ulcer "Steroid ulcers" Intestinal duplications

ACUTE OR SUBACUTE INTESTINAL OBSTRUCTION OF OBSCURE CAUSE

General considerations pertaining to x ray studies Unsuspected partial obstruction complicating prepyloric or duodenal ulcer "Pyloric channel ulcer" Concomitant gastric and duodenal ulcers Intra abdominal hernia formation Gallstone ileus Amyloidosis Scleroderma Cancer of the small bowel and mesentery Hypopotassemia Severe hypoproteinemia Plumbism Systemic lupus erythematosus Polyarteritis Hypothyroidism Spinal cord lesions Gastric cancer Duodenal obstruction by the superior mesenteric artery or an abdominal aortic aneurysm Muscle trauma to the back Acute pyelonephritis Ogilvie's syndrome Diverticulitis or intussusception of a Meckel's diverticulum Diverticulitis of the duodenum with perforation Small bowel polyposis Phytobezoars Prolapsed gastric polyps Obstruction by an adhesive band simulating pancreatitis Pneumatosis cystoides intestinalis Tuberculous enteritis Ameboma of the intestine Ascaris infestation Annular pancreas Aberrant pancreatic nodules Postpartum ileus Post traumatic intramural hematoma Posttraumatic mesenteric venous thrombosis Torsion of various intra abdominal organs Acute porphyria Myxedema Regional enteritis limited to the duodenum Endometriosis Herpes zoster

EXTRA ABDOMINAL CAUSES OF ABDOMINAL PAIN

PERSISTENCE or recurrence of abdominal pain after the patient has been subjected to an exploratory procedure for this very symptom has embarrassed every experienced and conscientious surgeon The list of the responsible underlying conditions in such instances is lengthy but deserves a place in this chapter In one study of abdominal pain Gordon found that 704 normal ovaries had been removed from 546 women in one year[13 7] Similarly in a pathological analysis of 2000 appendectomies it was found that one third of the appendixes removed from males and one tenth of those from females were normal

Over the years I have compiled a most impressive number of extra abdominal causes of abdominal pain that have either misled me my colleagues or other authors into pursuing a surgical approach[13 7, 13 8] This tabulation is set forth below with reference to the site of the source material elsewhere in the text but without further comment here

Constitutional Disorders

Diabetes mellitus (p 73)
Uremia (p 50)
Poisonings—lead arsenic mercury snake bites arachnidism methyl alcohol (pp 64–69)

Acute porphyria (p 61)
Lupus erythematosus (p 305)
Polyarteritis (p 307)
Hemochromatosis (p 60)
Hypothyroidism (p 16)
Addison s disease (p 13)
Hyperthyroidism (p 18)
Penicillin and other sensitivities (p 62)
Gout (p 74)
Essential hyperlipemia (p 78)
Periodic disease (p 412)
Primary amyloidosis (p 59)
Sickle cell disease (p 195)
Hemolytic crises (p 192)
Henoch s purpura (p 224)
Decompression sickness (p 218)
Pheochromocytoma (p 22)
Hyperparathyroidism (p 23)

Infections

Syphilis—tabetic crises (p 154)
The acute exanthemata
Rheumatic fever (p 310)
Brucellosis (p 156)
Leptospirosis (p 157)
Infectious mononucleosis (p 198)
Trichinosis (p 173)
Malaria (p 170)
Typhoid fever (p 163)
Hematogenous tuberculosis (p 150)
Salmonellosis (p 163)
Amebiasis (p 170)
Roundworm infestation (p 173)

Neurologic States

Polyneuritis—infectious metabolic (p 379)
Brain tumors (p 363)
Small strokes (p 359)
Migraine equivalents (p 358)
Postencephalitic states
Abdominal epilepsy (p 358)
Multiple sclerosis (p 356)
Schizophrenia (p 351)
Functional disease—depression hysteria the hyperventilation syndrome (p 351)

Affections of the Parietes

Spine—spondylitis metastatic disease myeloma spinal cord tumor (pp 310 185 and 376)
Subarachnoid hemorrhage
Meningitis
Epidural abscess (p 378)
Retroperitoneal disease—hematoma cold abscess tumor (p 184)
Hematoma of the rectus abdominus muscle
Incarcerated *epigastric* hernia

Herpes zoster (p 508)
The myopathies
Ileopectineal bursitis
Disease of the femur or hip
Abdominal aortic aneurysm—arterio clerotic dissecting (pp 298 and 295)

Urologic Problems

Torsion of the testicle or its appendix
Seminal vesiculitis (p 113)
Epididymitis
Dietl s crisis
Renal colic—stone hydronephrosis
Orchitis of an undescended testicle
Lipoid nephrosis—crisis (p 55)
Pyelonephritis (p 110)

Intrathoracic Conditions

Cardiac—coronary disease pericarditis aortic insufficiency congestive heart failure (pp 264 252 and 259)
Aorta—dissecting aneurysm aortitis (pp 295 and 299)
Lung pleura—pulmonary infarction with or without embolism pleurisy pneumonitis pneumothorax pleurodynia spontaneous interstitial emphysema (pp 212 265 and 451)
Diaphragm—eventration flutter (The sen ory innervation of the periphery of the diaphragm originates from the lower six intercostal nerves)
Mediastinum—infection tumor adenopathy (pp 336 and 455)
Esophagitis (p 455)

MASSIVE GASTROINTESTINAL HEMORRHAGE OF OBSCURE CAUSE

Attention is now directed to the frequent medical surgical problem of massive gastrointestinal hemorrhage of obscure causation The more common causes for such bleeding are usually well discussed in both the formal texts and in the frequent review papers which appear on this subject [13 9] It is almost superfluous to reiterate that peptic ulcer is responsible for fully two thirds of all the cases of gastrointestinal bleeding (Elderly patients with a bleeding peptic ulcer will not infrequently deny previous ulcer symptoms)

For purposes of orientation with regard to the relative incidence of the various causes of gastrointestinal bleeding the reader is referred to an analysis of 5192 cases that were recently culled from the literature by Gray, Olson and Manrique [13 9b] The following causes of bleeding were encountered in this review peptic ulcer—65 per cent, gastritis—11 per cent esophageal varices—9 per cent, gastric cancer—1 per cent hiatus hernia—2 per cent other causes—2 per cent, undetermined sites—10 per cent It is incumbent upon the clinician to search for other causes of bleeding in the patient who is found to have a hiatal hernia a gastric diverticulum, or a gastric polyp, which may only represent incidental findings

The occurrence of hematemesis will depend not only upon the actual site of the blood loss but also upon the rate of bleeding and the rate at which the stomach empties its contents If the rate of bleeding and motility

is excessive, there may be bright red melena from lesions as high as the small bowel As little as 50 ml of blood can produce a tarry stool (p 764) The infrequency of hematemesis from lesions below the ligament of Treitz has proved to be a useful aid for locating the bleeding

Throughout this text, various systemic causes of gastrointestinal hemorrhage have been cited These include the hematopoietic disorders (the leukemias, the lymphomas, polycythemia), malignant hypertension, polyarteritis, sarcoidosis, neurofibromatosis, elastica disease, neurologic diseases, and hyperparathyroidism A number of additional clinical considerations which recur with varying degrees of frequency in the analysis of these instances of undetermined gastrointestinal bleeding merit added attention and will be recounted here

1 Massive bleeding commonly results from an extensive *hypertrophic gastritis* or an *acute erosive gastritis* that may not be demonstrable by x ray or even with the gastroscope [1330] In this same regard, the author has found that upper gastrointestinal hemorrhage following a partial gastrectomy—in the absence of both symptoms and the roentgenographic demonstration of ulcer—is often caused by a gastritis or a jejunitis rather than by a recurring ulcer [1330c]

2 It is important to focus some attention on the duodenum beyond the cap in patients with suspected ulcer, since *postbulbar ulcers* pose a definite problem to all concerned, however infrequently they occur The clinical features of such ulcers do not differ much from other duodenal ulcers, except possibly in the greater associated incidence of massive bleeding and obstruction [1331] For example, in one series of 99 cases of postbulbar duodenal ulcer reported from the Mayo Clinic, there was a twofold increased incidence of hemorrhage [1331b] Instances of obstructive jaundice secondary to ulcers which affect the descending portion of the duodenum have been reported, but these are quite rare

3 In the absence of frank stomach or large bowel disease, the possibilities of *lesions of the small bowel* (congenital anomalies, tumors) and *nonspecific ulceration at the ileocecal area* must be considered and carefully pursued [1332] The presence of an associated distinctive melanin pigmentation is suggestive of *small bowel polyposis* (p 424) [1 50] Carcinomas and leiomyomas are more common in the upper part of the small intestine, whereas sarcomas and lymphomas occur in its lower portions with greater frequency

4 *Gastrointestinal bleeding resulting from intestinal duplication* usually occurs within the first three years of life (more than two thirds of the time in the first year) The small intestine is most often involved, with the hemorrhage tending to be quite severe in the case of long, tubular duplications of the ileum The bleeding may result from interference with both the arterial and venous blood supplies of the intestine, the effects of pressure upon the mesenteric blood vessels or the adjacent tissues, intussusception (with the typical currant jelly bleeding), or ulceration (if the duplication is also lined by gastric mucosa) A gastric mucosal lined duplication may involve practically the entire small intestine [1348b]

5 Massive gastrointestinal bleeding occurs infrequently as a result of a *uremic enterocolitis* On the other hand, it tends to complicate the course of the patient with acute renal insufficiency more often [1281c] In these in

stances, however, it is wise to consider the added possibility of the bleeding stemming from some associated lesion, such as acute peptic ulcers of the gastrointestinal tract, a traumatic hiatal hernia, or hemostatic defects

6 The various *poisonings* (especially from arsenic and bichloride of mercury) should not be overlooked in obscure cases of melena (pp 68 and 69) In the absence of other convincing possible causes or the recent ingestion of bismuth preparations the association of an acute necrotizing gastritis or jejunitis with radio-opaque material in the bowel is highly suggestive of acute arsenic intoxication—even when the renal findings are minimal [50] This condition might be diagnosed as an enterocolitis variously due to the *Staphylococcus*, the *Clostridia*, and the gram negative bacilli It has also been attributed to an adrenal crisis precipitated by an acute viral enteritis

7 No study of a puzzling severe anemia in adults is complete without ruling out blood loss from a *hiatal hernia* This is particularly important when "refractory' iron deficiency anemia affects females past middle age [1333] Another indication of the potential magnitude of this problem—even when anemia is absent—comes from a study at the Boston Lying In Hospital of patients with persistent gastrointestinal symptoms (particularly postprandial heartburn initiated or aggravated by lying down) in the latter part of pregnancy It was found that 62 per cent of these women had evidence of a hiatal hernia [1334]

It has been shown that there are three possible sources or modalities of bleeding associated with a hiatal hernia These include (1) a peptic esophagitis with superficial ulcerations (2) the Mallory Weiss type of lacerations, and (3) the chronic marginal ulcer [1335] In fact, the significant incidence of peptic esophagitis resulting from the reflux of corrosive gastric juices through an incompetent esophagogastric sphincter in the presence of a sliding type of hiatal hernia is now being stressed in many quarters [1335b]

8 The so-called *Mallory Weiss syndrome* consisting of erosions or lacerations in the long axis of the stomach and esophagus, should be suspected when hematemesis or a hemothorax follows a period of violent retching and *vomiting from any cause* [1336] Fleischner has stressed the fact that a hiatal hernia is usually a prerequisite for these esophageal lacerations [1335a] The lack of awareness of this relationship in the past stemmed from the inability of pathologists to detect small and medium sized hiatal hernias in the absence of frank incarceration

9 A chronic *peptic ulcer of the esophagus* may be superimposed upon heterotopic gastric epithelium or some variation of a congenitally short esophagus [1337]

10 If bowel bleeding occurs in the patient who is receiving *anticoagulant therapy* an *underlying gastrointestinal malignancy* must be seriously considered [1076]

11 Significant large bowel bleeding should be attributed to *diverticulitis* by exclusion *only* [1338] (Even so it is uncommon)

12 In the presence of extensive hypertensive or arteriosclerotic vascular disease, the occurrence of vague abdominal symptoms over a variable period of time followed by an acute abdominal crisis, progressive anemia and shock may be due to *ischemic infarction with subsequent hem*

orrhage into the liver[1339] A similar clinical picture could be due to a massive *retroperitoneal hemorrhage*, with or without an underlying aneurysm[1340]

13 Massive (and usually fatal) bleeding due to the *rupture of a saccular arteriosclerotic aneurysm* into the gastrointestinal tract—usually the third portion of the duodenum—is more common than is generally realized (p 298)[1341 1342] On the other hand, dissecting aneurysms of the aorta rarely rupture into the alimentary canal

14 As noted in a preceding chapter, particular care must be taken to exclude either *hemorrhagic telangiectasia* or *angiomas* of the bowel by a careful study of the skin and the mucous membranes (p 222)[813] While varicosities (phlebectasia) of the gastrointestinal tract are common in the rectum and esophagus, they may also occur in the small bowel, from which site hemorrhage can occur[1343 1344] Localizing this site of blood loss by means of the string test (p 754) might aid in excluding a bleeding duodenal ulcer There are infrequent instances in which severe bleeding from the mucosa of the bowel is due to *unusual localized capillary fragility* confined to the intestine[1343c] Examination of the resected surgical specimen (or autopsy) is the only means of establishing this diagnosis

15 The clinician should be reluctant to attribute bleeding to a *prolapse of the gastric mucosa into the duodenum* solely on the basis of its radiographic demonstration This finding is a normal physiologic phenomenon which the author feels has recently received undue attention as a cause of symptoms[1345] In several of these patients who have been explored, a concomitant gastric or duodenal ulcer was found[1346]

16 Similarly, it is very unusual for diverticula of the second or third portions of the duodenum to produce either bleeding or other symptoms This is in contrast to a *Meckel s diverticulitis* which presents in 75 per cent of the diagnosed cases as intestinal hemorrhage[1347a] Only in the very rare case does significant bleeding take place from a *benign ulceration occurring in a primary duodenal diverticulum*[1347b]

17 In addition to the possibility of hemorrhage from *jejunal diverticula*, attention is again directed to their possible etiologic relationship to the development of a megaloblastic anemia[701]

18 The diagnosis of *Henoch s purpura* should not be offered as an explanation for melena in infants and children until bleeding from a Meckel s diverticulum has been seriously considered (p 224)[1348a] There have been 25 cases reported to date in which actual *intussusception coexisted with Henoch's purpura*[816b] Although this particular combination is infrequent and difficult to define, the patient will die without surgical intervention There are very few reliable signs that would indicate the presence of an intussusception complicating an intestinal hematoma Both may individually result in a mass intestinal obstruction and melena

19 Chronic cholecystitis and cholelithiasis are described as unusual causes of *choledochal hemorrhage* resulting in melena[1349] This manifestation occurs more frequently, however, in chronic pancreatitis and pancreatic cancer On rare occasions, aberrant gastrointestinal mucosa has been found in the gallbladder (choristoma) following a laparotomy for massive gastrointestinal bleeding[1344] Cholecystectomy resulted in a complete cure

20 Significant gastrointestinal bleeding is present in 15 per cent of

patients with *pancreatic cancer* A number of factors may be involved in the pathogenesis of such bleeding These include local gastrointestinal metastases, increased portal vein pressure, hypersplenism and defects in the blood coagulation mechanism (p 329)[1041-1045]

Recurrent acute pancreatitis has been observed to exert sufficient compression upon the portal vein as to result in portal hypertension and subsequent hemorrhage from esophageal varices[1353]

It has been the experience at the Lahey Clinic that *duodenal ulcer coexists with chronic relapsing pancreatitis* in more than 15 per cent of these cases[1353b] This observation is accordingly of considerable importance when gastrointestinal hemorrhage occurs in the presence of the latter disorder

21 It is estimated that up to 15 per cent of *esophageal varices* will disappear roentgenographically if the patient survives the first bout of bleeding and then follows intensive medical management Dilatation of the veins in the fundus of the stomach frequently antedates the demonstration of esophageal varices in portal hypertension These vessels can also account for massive bleeding In fact the *gastric varices* may reach such a large size that a gastric neoplasm is usually suspected should the esophageal varices not be seen[1350] If doubt still exists as to the source of the active bleeding—particularly in the absence of the other late manifestations of cirrhosis—the degree of BSP retention often serves as a safe and reliable diagnostic aid (p 716)[1351] (One should bear in mind when interpreting abnormal retention of sulfobromophthalein following a massive gastrointestinal hemorrhage that the anoxia resulting from the blood loss *per se* might account for such retention in the presence of a normal liver)

Clinicians must always be cognizant of the fact that patients with cirrhosis of the liver not infrequently bleed from a concomitant peptic ulcer[3 5] In addition Palmer has shown that an erosive gastritis—gastroscopically and histologically identical with that encountered in the absence of liver or portal disease—occurs in portal hypertension[135 b] He has postulated that a circulating metabolite (rather than the mechanical venous back pressure) or mucosal hypoxia stemming from activity in the gastroduodenal shunt system may be the basis for such a lesion

It is not generally appreciated that significant melena in the presence of *portal hypertension* can result not only from bleeding of esophageal and gastric varices, but also from the *varicosities in the omentum the bowel*, and *the peritoneal surfaces* due to this same cause[135] Massive gastrointestinal bleeding has taken place from the penetration of serosal varicosities on the cecum and ascending colon into the colon[135]

22 The subject of *drug induced peptic ulcer* has assumed increasing importance in recent years The reader is referred to the recent comprehensive review by Kirsner[1355c] Several of these noxious drugs will now be specifically cited

Upper gastrointestinal hemorrhage following the ingestion of *salicylates* is neither unusual nor infrequent[1354] These compounds may reactivate a previously dormant peptic ulcer through various mechanisms (local irritation, gastric allergy hypoprothrombinemia pituitary adrenal stimulation leading to hyperacidity) In fact, such a sequence can partially account

for the characteristic seasonal incidence of ulcer (i e , in the spring and fall, coincident with the majority of colds) In most patients with salicylate induced gastritis, however repeated bouts of painless bleeding are not associated with the roentgenographic evidence of an ulcer

Several reports have strongly implicated the development or recurrence of an acute duodenal ulcer following the prolonged or intensive use of *reserpine* therapy [1355]

Three other therapeutic agents whose administration may be complicated by the development or reactivation of peptic ulcer in susceptible individuals are *phenylbutazone, the adrenal steroids,* and *corticotropin* (*vide infra*) [1358]

23 The presence of extensive calcification in the mediastinal or abdominal lymph nodes in a patient with gastrointestinal hemorrhage may serve as a clue to the perforation of either a *tuberculous node or a false aneurysm* complicating this type of adenopathy The esophagus, the duodenum, and the jejunum have been the most frequent sites of such bleeding A tuberculous enteritis need not be present [540, 541]

24 In 3 of 12 patients with *extensive amyloidosis*, fatal massive gastrointestinal hemorrhage occurred [193] Even in those patients in whom bleeding did not take place, some degree of involvement of the submucosal vessels in the gastrointestinal tract was observed

25 Massive gastrointestinal hemorrhage is encountered in *elastica disease* (the Gronblad Strandberg syndrome, "hereditary elastodystrophy"), particularly in pregnant women with this unusual disorder (p 314) [986, 988] A careful search for the presence of pseudoxanthoma elasticum in the skin or angioid streaks in the retina can confirm this diagnosis

The cutaneous manifestations of pseudoxanthoma elasticum are depicted in Figure 74 (Atlas page 46)

26 The diagnosis of bleeding from or perforation of an abdominal viscus in a young woman should be made only after *intermenstrual pain (mittleschmerz), a ruptured corpus luteum,* and *endometriosis* have been seriously considered [1356]

27 *Injury to the rectum caused by previous irradiation* (factitial or radiation proctitis) particularly when directed to the cervix, is another source of rectal bleeding The magnitude of the hemorrhage may be of any order [1357] The intrarectal insertion of hydrocortisone in a water soluble jelly has been advocated for this complication

28 The frequent recurrence of symptomatic peptic ulcer in a cooperative patient who has followed an intensive therapeutic regimen should suggest the possibilities of (1) an underlying *hyperparathyroidism* (p 23),[69, 74] and (2) *alpha or beta cell tumors of the pancreas* (p 20) [63, 66] Similarly, the finding of multiple ulcerations in the stomach, duodenum, and jejunum at the time of surgery should make the surgeon very suspicious of an associated pancreatic adenoma This is particularly true when stomal ulcers subjected to strict medical management postoperatively remain resistant to such therapy [63]

29 The incidence of *Curling's ulcer* in severely burned patients is significant This complication may be asymptomatic, or it may be manifested by massive bleeding and pain In one series of 1000 burned patients,

such gastrointestinal ulceration (usually of the duodenum) occurred in 20 individuals Twenty one per cent of the patients who died exhibited this lesion[1361a] This is not an academic matter, inasmuch as intensive prophylactic antacid therapy under these circumstances might obviate the great hazard that emergency surgery would incur

Similarly, "stress' peptic ulcers with massive hemorrhage have been observed in a number of neurologic disorders,[1030] and following operations or trauma not directly involving the stomach[1361b]

30 The increasingly important subject of '*steroid ulcers* merits specific attention These lesions probably stem more from the dissolution of connective tissue and a depression of the repair processes than from the excessive gastric secretion of acid and pepsinogen Gastrointestinal bleeding should be anticipated in *every* patient with induced hyperadrenalism resulting from the therapeutic use of large amounts of corticotropin or the adrenocortical steroids on a long term basis[1358] This is particularly true of the compounds related to prednisone, which appear to be more ulcerogenic The long term experience in several large series of patients with rheumatoid arthritis who were so treated indicates the occurrence of these sequelae in as high as 25 per cent of the cases Symptoms of ulcer and bleeding usually begin after the second or third week They have been noted however, as early as three days

'Giant' bleeding ulcers are also being encountered with increasing frequency in patients with ulcerative colitis and regional enteritis who are maintained on large doses of these steroids[1358] (On the other hand, some gastroenterologists believe that giant ulceration is related more to the severity of the ulcerative colitis They further claim that such lesions may actually respond favorably to the corticoids)

Although the incidence of chronic peptic ulcer in adrenal insufficiency is very low, cases of both ulcer arising *de novo* and reactivation of a previous ulcer have been demonstrated in patients with Addison s disease following the institution of cortisone replacement therapy[1359] It is also not amiss to recall that individuals with emphysema have a greater incidence of peptic ulcer or hypertrophic gastritis but rarely experience the typical ulcer pain[1360] Accordingly careful observation along with antiulcer precautions are necessary when hormonal therapy is employed in this situation

ACUTE OR SUBACUTE INTESTINAL OBSTRUCTION OF OBSCURE CAUSE

The astute internist or radiologist may be of considerable assistance to the surgeon in the latter s orientation to the problem patient with acute or subacute intestinal obstruction As in the case of gastrointestinal hemorrhage the usual differential diagnosis is omitted here since it is assumed that the reader is well aware of the more frequent causes of small and large bowel obstruction (i e adhesions, tumors mesenteric vascular occlusion, and the sequelae of hernia)

A few introductory remarks pertaining to a number of considerations that recur in the *x ray study of mechanical and paralytic ileus* are in order[1362] In contrast to the use of the barium swallow there are few con-

traindications to the careful performance of a barium enema, even when bowel obstruction is actually suspected The use of the water soluble contrast media that are employed in urography and in angiocardiography offers a safe method for making preliminary studies in those patients for whom the ingestion of barium sulfate suspensions might prove to be hazardous[1363] This could be most important in instances of suspected obstruction involving the small bowel This particular method can also be used to advantage where barium enemas might pose somewhat of a risk, as in suspected intussusceptions

Films showing both supine and upright positions should be obtained initially, the latter to demonstrate dilated loops of bowel and fluid levels (Enemas are to be avoided, since the ensuing fluid retention could simulate fluid levels) The following considerations should be borne in mind (1) considerable air may be present in the small bowel of a patient with renal colic acute pancreatitis, and other acute extraenteric conditions, and (2) air introduced into the peritoneal cavity is almost always absorbed by the second or third week[13 0] In fact, the finding of a regional or reflex ileus in the survey abdominal film is often a very valuable clue as to the presence of disease in that area For example, the presence of gas filled bowel in the right upper quadrant may point to an acutely enlarged gallbladder Reflex ileus is also of value in the detection of perforated ulcer, pancreatitis, appendiceal abscess, and other acute disorders[1362a]

While the preservation of the valvulae conniventes is usually a helpful sign in differentiating dilated loops of small and large bowel, this could prove to be misleading in the case of a dilated ileum Although they are at times quite suggestive,[769] most observers feel that the dilatation and other changes of those areas of the bowel which are supplied by either the superior or inferior mesenteric arteries and veins are not sufficiently diagnostic of thrombosis involving these vessels A careful study of the properitoneal and retroperitoneal fat lines may be most rewarding This is particularly true when their disappearance is localized, should there be any difficulty in distinguishing ileus from peritonitis

Chest films should also accompany the anteroposterior and lateral films of the abdomen and pelvis both for their diagnostic value and as a baseline reference for possible postoperative complications[1 6 0] The "cleavage planes' that are seen in the lateral view of the abdomen and pelvis are usually well defined Their absence may be of considerable aid in the diagnosis of inflammatory complications within the pelvis It is stressed that the diagnosis of a pelvic tumor must never be made on the basis of x rays until the physician is certain that the bladder was emptied The radiolucency of certain dermoid tumors may be mistaken for gas shadows in the intestines[136 0]

On the basis of his own experience both in practice and in consultation, the author has come to regard *partial obstruction complicating benign prepyloric or duodenal ulcer* as one of the most frequently misdiagnosed disorders of the gastrointestinal tract[1364] This condition must be constantly borne in mind in the presence of the so-called intractable ulcer, *whether nausea and vomiting are present or absent* Furthermore, intensive anticholinergic therapy should be withheld until this complication has been

definitely ruled out, inasmuch as the major effect of such treatment is to produce further paresis of the already distended and partially atonic gastric musculature In addition to the measurement of postprandial gastric retention the gastric succussion splash (or "clapotage) is a most useful diagnostic aid at the bedside [1364b]

A similar consideration applies to the more acute *"pyloric channel ulcer* This entity may be readily mistaken for psychic vomiting carcinoma of the stomach and gallbladder or pancreatic disease when atypical pain and significant weight lo s dominate the clinical picture [1365a] It is pointed out that the amount of barium retained after a barium swallow is not only an index of the pyloroduodenal stenosis but also of the gastric tone and motor power [1364] Consequently if the gastric tone is good and peristalsis is very active one may see no retention—even in the presence of considerable stenosis It should be appreciated that the so-called pyloric-channel ulcers do not constitute a homogenous group but can include prepyloric gastric ulcers, duodenal ulcers and pyloroduodenal ulcers Consequently the designation peptic ulcer near the pylorus" is probably preferable [1365b]

Reference has been previously made throughout this book to such possible causes of intestinal obstruction as the lymphomas (p 181), endometriosis (p 345), the dyscollagenoses (pp 304 to 307), hypokalemia (pp 79 and 477), regional enteritis (p 49) diverticulitis (p 761), appendicitis (p 488), lymphogranuloma inguinale (p 155) and occlusion of the mesenteric ve sels (p 214) Several additional interesting causes of this condition that should also be occasionally considered will be enumerated below

1 When considerable gastric retention occurs in the presence of a *large gastric ulcer* it is wise to look for evidence of a *concomitant active or healed duodenal ulcer* In a review of 135 instances of this phenomenon, Johnson observed that the ulcers do not behave as do other gastric ulcers, but are prone to be very large deep and resistant to treatment [1366]

2 *Intra abdominal hernia formation* and the subsequent incarceration of bowel can take place in a number of vulnerable sites Among these are the paraduodenal fossae the foramen of Winslow the cleft in the mesentery of the sigmoid, the pericecal area the esophageal hiatus or the pleuroperitoneal hiatus, and postoperative defects in either the omentum or the mesentery [136] The alert radiologist may be able to suspect the diagnosis on a plain film by noting a segmented gas shadow

3 The presence of unexplained intestinal obstruction, most notably in the lower portion of the small bowel should alert the clinician to the possibility of a *gallstone ileus* [1367] The demonstration of a cholecystenteric fistula—either by the presence of air in the biliary ducts or by the entrance of opaque medium into the biliary ducts following a barium swallow—adds considerable weight to this consideration Many gallstones are not radioopaque, particularly when they are composed of cholesterol

Prolonged observation with the hope of a spontaneous cure is attended by an alarmingly high mortality rate in this disorder Furthermore, there have been a number of instances in which a second operation was necessitated because of recurrent gallstone ileus [1367b] The small intestine should

be accordingly examined from the ligament of Treitz down to the ileocecal valve for stones during the initial procedure, and a cholecystectomy or a cholecystostomy performed for the removal of stones, depending on the patient's condition The search for additional gallstones should be routine when facets are found on a gallstone that has been causing obstruction Particular attention to the retroperitoneal duodenum is in order when there is the possibility that other stones are present, since this is a readily overlooked area in which stones might become sequestrated

4 The presence of chronic small bowel distention with very slow motility and a poor response to parasympathomimetic drug stimulation should make one suspicious of the following possibilities *amyloidosis* (p 59), *scleroderma* (p 309), *cancer of the small bowel and mesentery hypokalemia* (p 79), and *severe hypoproteinemia* [1368]

5 The occurrence of progressive subacute or chronic constipation in the absence of demonstrable disease of the small or large bowel might also alert the clinician to the possibilities of *plumbism* (p 65), *systemic lupus erythematosus* (p 305), *polyarteritis* (p 307), *hypothyroidism* (p 16) *and spinal cord lesions* (p 374) It would behoove the physician under similar circumstances to recall that a striking change in bowel habit frequently occurs as a manifestation of *gastric cancer*

6 Obstruction of the third portion of the duodenum from the *pressure exerted by the overlying superior mesenteric artery* may be misinterpreted as resulting from either adhesions or a paraduodenal hernia The occurrence of *intermittent upper abdominal cramps in an asthenic*, lordotic patient—especially if precipitated by large meals and relieved by vomiting or lying down—is highly suggestive of this disorder [1369] Clinicians must not hasten to subject these patients to surgery, however In many instances, the arteriomesenteric obstruction is primed by the duodenal dilatation that occurs as a result of chronic nutritional and emotional disturbances (Duodenal ileus is very common in anorexia nervosa) The presumed obstruction may accordingly disappear without the necessity for any surgical intervention if these factors are treated and the duodenal tone restored Considerable obstruction of the duodenum can be also produced by an *abdominal aortic aneurysm* (p 298)

7 A number of patients presenting with severe ileus or an acute abdominal crisis (even with fever and leukocytosis) *following simple muscular trauma to the back* have come to the author's personal attention

8 The peritoneal irritation resulting from the retroperitoneal inflammation of an unrecognized *acute pyelonephritis* has induced a paralytic ileus of sufficient magnitude to lead to a laparotomy (p 111)

9 Similarly, *infiltration of the autonomic nerves in the retroperitoneal area*, either by tumor or by blood, may be associated with suggestive or actual intestinal obstruction This condition is known in the British literature as *Ogilvie's syndrome* [906, 1370] In this regard the retroperitoneal hematoma associated with an acute hemorrhagic pancreatitis has been known to have resulted in pyloric or high intestinal obstruction [1 140]

10 Subacute intestinal obstruction resulting from either *the diverticulitis or intussusception associated with a Meckel s diverticulum* is occasionally encountered in adults The symptom complex in such instances has

been variously diagnosed preoperatively by eminent clinicians as regional enteritis, an intussuscepting submucous lipoma of the small bowel and gastrointestinal wheat allergy—in addition to the commoner causes of small bowel obstruction[1372] Several cases are on record in which stones resembling gallstones have formed within the diverticulum itself[1372b] The preoperative radiographic diagnosis of a Meckel s diverticulum is *rarely* made indeed, when this structure is filled with barium it is usually regarded as a loop of small bowel[13 d] A distinct cherry red cellulitis involving the umbilicus and its surrounding circumference is considered specific for a Meckel s diverticulitis[137] This is infrequently seen however, since the fibrous cord connecting the umbilicus and the intestine, along with its associated blood vessels persists in less than 20 per cent of these patients

11 *Diverticulitis of the duodenum with perforation* can simulate a high intestinal obstruction as well as peptic ulcer and diseases of the biliary tract or pancreas[1371] It may be missed at the time of a laparotomy if care is not taken to examine the adjacent retroperitoneal tissues for evidence of free air, bile staining and edema

12 The characteristic osteomatosis and spotty melanin pigmentation of the skin and mucous membranes that occur in the *Peutz Jeghers syndrome* should be sought for in the patient who is experiencing periodic postprandial midabdominal colic These findings, particularly when associated with recurrent intussusception, peripatetic abdominal masses, melena and anemia are highly suggestive of the concomitant *small bowel polyposis* (p 424)[1250 1252]

The cutaneous manifestations of the Peutz Jeghers syndrome are depicted in Figure 2 (Atlas page 3)

13 *Phytobezoars* resulting from the ingestion of vegetable and plant material of certain types (particularly persimmons) are smaller than trichobezoars (masses of hair) and are more prone to cause obstruction of the small bowel[1150] A history of the excessive use of bran for breakfast in the presence of small bowel obstruction and previous abdominal surgery should suggest the possibility of desiccated bran as the basis for the obstruction[1373]

14 *Benign gastric polyps* and *polypoid carcinomas* can *prolapse into the duodenal bulb* The fortuitous demonstration of a thick pedicle either proximal to or occupying the pyloric canal is obviously of considerable diagnostic value in such instances

15 It is well known that *acute (hemorrhagic) pancreatitis*—even in the absence of a retroperitoneal hematoma[1374]—commonly produces a severe paralytic ileus within a short time after its onset On the other hand most clinicians and surgeons do not appreciate the fact that an occasional patient with *small bowel obstruction* (either high or low) and gangrene caused by an *adhesive band* may present with the identical picture (i e , an elevated blood amylase, a low serum calcium peritoneal serosanguinous fluid, and livedo reticularis) which is not primarily due to dehydration electrolyte imbalance or prerenal azotemia[1374] It is postulated that when the duodenum becomes distended from mechanical obstruction, it can create a pressure within the pancreatic-duct system of sufficient magnitude to produce a mild interstitial pancreatitis with an elevated blood amylase

(Clinicians and surgeons should furthermore note that the findings of shock, high serum amylase titers, hypoglycemia, and lowered serum calcium levels in the presence of an abdominal crisis have also been encountered in patients with unrecognized perforated peptic ulcer and with mesenteric infarction)[13 2c]

An illustration of livedo reticularis associated with acute pancreatitis appears in Figure 96 (Atlas page 62)

One of the most consistent x ray findings in patients with pancreatitis is a persistent or intermittent narrowing at or near the splenic flexure, in association with significant distention of the large bowel proximal to that point [1374d] There may or may not be associated distention of the small intestine The importance of differentiating these changes from various tumors, inflammations, vascular thromboses, and adhesions of the bowel is evident

16 Partial obstruction of the large bowel has been caused by *pneumatosis cystoides intestinalis* The alert radiologist or clinician can differentiate this entity from multiple polyposis and carcinoma both on the plain scout film and after the introduction of opaque contrast medium, particularly by observing the flattening at the base of the gas cysts when the bowel is distended The condition may be primary, or it can be secondary to gastric or duodenal ulcers, enteritis, recent intestinal operations, and intestinal parasitism [1375a]

17 Very large air filled diverticula can develop from cystic dilatation of a pulsion diverticulum of the sigmoid, a Meckel s diverticulum, or a congenital duplication of the bowel [1 5b]

18 The development of increasing obstipation and a right lower quadrant mass in the patient with advanced pulmonary *tuberculosis* may be due to ileocecal involvement by this infection, particularly of the hyperplastic type Mucosal irregularities, spasm, and deformity of both the terminal ileum and cecum are found on x ray The so-called "crow's beak deformity" due to the resulting deformity at the tip of the cecum an epsilon like appearance, and Stierlin s sign (viz a gap in the cecal shadow when the ileum and colon are filled) have also been described It is well to bear in mind that *carcinoma regional enteritis, amebic cecitis, an edematous, lipomatous, or hypertrophied ileocecal valve*, and *ileal prolapse* can all produce similar roentgenographic patterns [1376] Brief mention is made of *tuberculosis of the appendix* This disorder may persist over long periods of time and is usually brought to the surgeon's attention following a superimposed infection of this organ [1376c]

19 A careful search for *Entamoeba histolytica* in the stools is in order when an unusual case of intermittent intestinal obstruction with an abdominal mass presents itself (p 170) Of 119 patients with *ameboma of the intestine* whose cases were reviewed by Radke, 41 died, of these, only 8 had received specific antiamebic therapy [616] While combined treatment with atabrine and carbarsone frequently relieved the obstruction, this complication was first observed in several instances during antiamebic therapy

20 The seriousness of small intestinal obstruction caused by *Ascaris infestation* is not generally appreciated This observation is evidenced by

the mortality of 33 per cent in two recent series of 10 and 18 patients with this condition [6 5] Volvulus strangulation, perforation, peritonitis, and even hepatitis, obstructive jaundice, or pancreatitis from the ductal invasion of the parasites have been reported A characteristic roentgenographic picture may be noted, consisting of closely packed, short irregular wisplike radiolucent lines in a somewhat parallel arrangement within the more dense mass of ascarides While the use of piperazine citrate (Antepar) and hexylresorcinol may be curative and obviate surgery—particularly where the intestine is not dilated or completely obstructed—there are known instances of recurrent obstruction after such nonoperative treatment Since the performance of an enterotomy is often both difficult and septic resection of the obstructed intestine with double enterostomies (which can be closed later) is recommended [6 5a]

21 The differential diagnosis of a constricting lesion in the descending portion of the duodenum with proximal duodenal dilatation should include the presence of an *annular pancreas* both in infants and adults Drey has reviewed 60 adult cases of symptomatic annular pancreas from the world literature and 2 of his own with particular emphasis upon the clinical separation of the adult and the pediatric forms [1378a] He calls attention to the nocturnal aggravation of the pain and vomiting as important diagnostic clues presumably due to the angulation and obstruction of the dilated proximal duodenum Similarly emphasis is placed upon the usually good nutritional state of these patients notwithstanding the five year average duration of symptoms The duodenum tends to be retracted toward the pancreas at the level of the annulus with mucosal effacement and dilatation of the duodenum The pathognomonic double bubble sign in the very young is of little value in adults however [1378b] An annular pancreas is most apt to be confused with neoplasms and postbulbar ulcers

21 Although *aberrant pancreatic nodules* within the duodenum and the stomach were reported in up to 13 7 per cent of a large series of consecutive autopsies, the condition is usually asymptomatic with comparatively few complications ensuing Various symptoms may be related to the occurrence of stenosis, spasm ulceration inflammation cyst formation, *occlusion of the papilla of Vater and the effects of tumor formation* (i e, hyperinsulinism, obstruction intussusception) [54 1379]

22 While mild degrees of *ileus* are not infrequently encountered *in the postpartum period* severe obstruction of the large bowel and small bowel can occur This complication has been noted following delivery both by the normal route and after cesarian section [1380a] In the latter instance one may be contending not only with pre existing bands or adhesions but with the following (1) the movement of a portion of the greater omentum which is attached to the uterus into the pelvis concomitantly with the involution of the uterus possibly obstructing a loop of bowel en route (2) acute kinking of a segment of the small bowel which may have become attached to the uterine scar (3) the pressure of the enlarged uterus on the sigmoid at the pelvic brim and (4) the extremely rare *ileus of pregnancy* characterized by paralysis of the smooth muscle of the bowel A cecal volvulus is apt to result after section in the presence of a mobile mesen

tery of the cecum Detorsion of such a postpartum volvulus has been effected by the assumption of the knee-chest position [1380b]

23 *Intramural hematoma* is a rare consequence of nonpenetrating injuries to the abdomen, and can result in either partial or complete intestinal obstruction Obstruction from this cause has occurred at intervals ranging from a few hours to several days, depending on the rate of increase in the size of the hematoma It is most apt to be found in the relatively fixed portions of the gastrointestinal tract (as is the case with other nonpenetrating injuries) Simple evacuation of the clot will usually suffice, although an enterocolostomy may be necessary in the more extensive lesions [1381a]

24 Another complication that may follow *nonpenetrating traumatic injuries* to the abdomen and lead to ileus is that of *mesenteric venous thrombosis* [1381b] In this instance, the ensuing intestinal infarction can take place immediately after the traumatic insult, or it may be delayed for as long as five weeks

25 In the presence of acute abdominal episodes characterized by a bizarre picture of ileus and pain, one might give some thought to the possibility of a *torsion of some intra abdominal organ* about its small base or pedicle Several of these possibilities will be cited below

Volvulus of the colon, particularly the cecum[1377b, 1380b] and sigmoid[1377c] accounts for 3 per cent of all the cases of large bowel obstruction The aberrant locations of the gas filled segments of distended bowel that has been subjected to volvulus could prove to be misleading for the less experienced [e136] The two following instances are cited in this regard (1) the presence of the cecum in the left upper quadrant when volvulus of this organ has taken place (the diagnosis might also be suspected by the absence of gas or fecal residue shadows in the right iliac fossa), and (2) in volvulus of the sigmoid, the gas distended segment can be visualized in the right abdomen [136 e]

Volvulus of the transverse colon is very rare if the various anomalies of rotation are excluded (i e , nonrotation, malrotation, reversed rotation) When it is encountered, it is found that the transverse colon is usually participating in an internal or external hernia, particularly postoperative tears within the mesocolon [1377i]

Surgeons must always be aware of the fact that in up to 50 per cent of cases of volvulus of the cecum, there may be other organic disease involving the large bowel distal to the site of the cecal torsion [1377k] While the acute nature of such a volvulus obviously requires prompt surgical attention, barium enemas and special studies of the large bowel should be performed in the postoperative period to ascertain whether possible associated pathologic conditions may be present (viz , carcinoma of the colon, diverticulitis, strictures)

Volvulus of the long afferent loop following a subtotal gastrectomy and a Polya antecolic gastrojejunostomy [13 40, 1377d]

Torsion of a Meckel's diverticulum

Torsion or infarction of an epiploic appendage, reviewed in 123 cases, was diagnosed correctly only once (in a patient who had had an appendectomy previously) [1377e]

A similar situation exists in the case of *idiopathic spontaneous segmental*

infarction of the greater omentum, which is almost universally mistaken for acute appendicitis or acute cholecystitis [1377f, g]. This entity should not be confused with the generally recognized condition of torsion of the greater omentum. Unlike the situation in acute appendicitis, peristalsis is usually normal, distention may be minimal, and the pain is very localized. Since many of these individuals are obese, it has been postulated that the omental veins might be stretched by the increased gravitational pull of an extremely fatty omentum, leading to endothelial injury with subsequent thrombosis and infarction. It is also interesting to speculate that certain instances of unexplained intestinal obstruction may actually result from the effects of previously unrecognized omental infarcts.

Torsion of a genital tract appendage, particularly pedicled uterine leiomyomas and ovarian cysts or tumors [137a].

Acute volvulus of the stomach is a rather infrequent surgical emergency that is mentioned because of the possible hazards in preoperative management that might arise. Clinical symptoms usually take place only when the torsion exceeds 180 degrees (since there is little obstruction or strangulation of the gastric blood supply when the stomach is twisted less than 180 degrees). The typical case will present with the so-called Borchardt and Lenormant triad that consists of the following: (1) vigorous efforts to vomit without success, (2) circumscribed epigastric pain with severe aching in the back, and (3) the inability to pass a stomach tube [1377h, i]. The latter maneuver and the ingestion of baking soda are both potentially very hazardous in this situation.

Lasky and Lichtenstein have reviewed the various contributory factors to volvulus of the stomach [1377i]. In practically all the cases, some anatomic anomaly can be found that renders the stomach susceptible to displacement, particularly the failure of fusion of the greater omentum with the transverse colon. One might suspect this condition roentgenologically from the following observations: localized massive distention in the upper abdomen, visualization of the "hairpin loop" with the incisura being directed to the right upper quadrant or posteriorly, fixation of the loop irrespective of whether the patient is in the decubitus or the Trendelenburg position, the delimitation of the barium in a tapered extremity of the esophagus, and possibly an anterior or inferior deviation in the position of the spleen.

26. It is generally appreciated that both bowel distention and abdominal pain can be striking features of *intermittent acute porphyria*, and that the degree of obstipation and x-ray changes in the abdomen may simulate a bowel obstruction (p. 61). On rare occasions, however, the disturbed motor function of the bowel caused by this metabolic derangement is sufficient to induce a true volvulus or intussusception and strangulation for which surgical intervention is mandatory. This course of action is particularly in order if a weakening pulse and the inflammatory signs cannot be explained by dehydration and electrolyte depletion alone [219b].

27. In addition to the well known symptoms of constipation, flatulence and mild distention, there may be marked ileus and even a megacolon-like syndrome associated with *myxedema* (p. 16) [26]. Pathologic studies of the wall of the colon have revealed thickening, loss of elasticity, and

a consistency of soft leather. The administration of thyroid substance will induce a prompt remission.

28. *Regional enteritis* may be *limited solely to the duodenum* or it can occur concomitantly with involvement of the other portions of the small intestine as well (p. 49). It is apparent that when nausea and vomiting are due to isolated involvement of the duodenum, a host of diagnostic possibilities might arise.[166] Although the sequence is most unusual, a volvulus has been known to complicate the course of regional enteritis.[168d]

29. *Endometriosis* should be considered in any young female patient with unexplained bowel obstruction. Although it involves chiefly the rectosigmoid area, practically all other areas of the bowel have been invaded. In addition to the exaggeration of symptoms at the menstrual periods, the following radiographic signs may be helpful: an intact mucous membrane, fixation, the absence of tenderness before or after the menses, a concentric, stenosing, or polypoid lesion, usually sharply demarcated, and with an otherwise normal bowel, and only a short length of involvement (usually less than 6 cm.) (p. 345).[106f, g]

30. Acute intestinal obstruction has complicated the course of *herpes zoster*, even to the extent of causing localized, spastic inflammatory changes in the bowel by x-ray.[1381c] This complication presumably represents the direct involvement of the bowel by this virus rather than the reflex irritation of the postganglionic sympathetic fibers of the autonomic nervous system. Surgical intervention in such cases is both unnecessary and undesirable (assuming that the infection does not represent the dermadrome of an associated bowel malignancy).

GROUP XVII

Cutaneous Medicine

INTRODUCTION

DERMAL CLUES TO SYSTEMIC DISEASE

Pigmentations and Color Changes

Melanosis—differential diagnosis Argyria Carotenemia Sulfhemoglobinemia Methemoglobinemia

The Erythemas and Purpuras

Pruritus

The Xanthomatous Lesions

Herpes and Herpetiform Eruptions

The Photodermatoses

Tumors and Nodule

Nail Changes

Miliaria and Anhidrosis

Hypertrichosis

The Tongue as an Indicator of Systemic Disease

SYSTEMIC DISEASES AND THEIR ASSOCIATED DERMADROMES

The Endocrinopathies

Metabolic Disorders

Systemic Intoxications

Liver and Biliary Tract Disorders

Hematologic Diseases

Neoplastic Diseases

Disorders of the Nervous System

Neurologic disorders The psychoneuroses

The Collagen Disorders

Infectious Diseases

Miscellaneous Dermadromes

Gastrointestinal disorders Respiratory disorders Rheumatic diseases Cardiovascular disorders Peripheral vascular disorders Sarcoidosis Calcinosis cutis Progressive lipodystrophy Chronic radiodermatitis Sjogren's syndrome The germinal dysplasias Angiokeratoma corporis diffusum universale Acrodermatitis chronica atrophicans Poikiloderma atrophicans vasculare

A PICTORIAL ATLAS OF SYSTEMIC DERMADROMES (*Opposite page 514*)

INTRODUCTION

THE SKIN (which is, in a sense, actually the largest organ of the body) is physiologically associated intimately with the other structures and systems through nervous, circulatory, and endocrinal interchanges—as well as by its contiguous relationship with the underlying tissues For this reason, *it is often a rather sensitive reflector of both normal and pathologic states*

Throughout all sections of this book, reference has been repeatedly made to the numerous important cutaneous manifestations of systemic disease This approach was emphasized in particular in the discussions of the neoplastic disorders, the lymphomas and leukemias, and the chapter on metabolic derangements The atypical pigmentations of hemochromatosis, porphyria, myxedema, uremia, jaundice, carotenemia, pernicious anemia, drug effects and hemoglobin products (methemoglobin, sulfhemoglobin) can all contribute significantly to the perplexing nature of their associated syndromes Weiner has aptly referred to these dermal components of underlying systemic diseases as "dermadromes"

The diagnostician should avail himself of every opportunity to become familiar with "cutaneous medicine" *Such an effort will continually alert* him to the rewarding concept that dermatopathology is in reality a window to internal disease" The ramifications of this truism extend not only to the aforementioned spheres of the malignant diseases and the metabolic disorders, but also into the reticuloendothelioses, the dyscollagenoses, the endocrinopathies the infectious diseases the granulomata, and many hematopoietic derangements It is apparent that the conscientious dermatologist can no longer be the morphologist or "externist" of *several decades* ago His responsibilities and those of the internist frequently overlap and require careful correlation for the prompt diagnosis and correct *treatment* of the many systemic diseases that evoke these *dermadromes*

It is virtually impossible for physicians who lack a good background in dermatologic diagnosis to be able to define accurately the cutaneous manifestations of systemic diseases since they are apt to confuse obvious instances of rosacea or seborrheic dermatitis with lupus erythematosus, all dark lesions of the skin with melanomas and most scaling eruptions of the hands and feet with the mycoses Three other common examples will also be cited below *In addition to this morphologic familiarity*, a comprehensive insight into the normal physiology chemistry, bacteriology, and pigment mechanisms of the epidermis the corium the subcutaneous tissues, the hair, the nails, and the sweat glands will impart to the clinician a considerable advantage in medical diagnostics

No detailed discussion of the "primary" dermatologic disorders (e g, psoriasis, lichen planus pityriasis rosea, and pemphigus) will be attempted in this chapter One cannot minimize the importance of a high degree of familiarity with these entities if any proficiency is to be achieved in defining the various expressions of systemic disorders on the skin in view of the frequent great similarity of their morphologic expressions *The following* three instances will be set forth for emphasis

1 The differential diagnosis of *lichen planus* could include much of dermatology in itself Some of the systemic disorders that must be considered include drug eruptions, neurodermatitis amyloidosis, and Kaposi's idiopathic hemorrhagic sarcoma The frequent lesions in the mucous membranes could simulate those encountered in leukoplakia syphilis, and lupus erythematosus

2 Similarly, it is vital to distinguish *pemphigus vulgaris* from a number of other systemic disorders and primary bullous disorders of the skin in view of the effectiveness of the corticosteroids in treating the former Some of these conditions include dermatitis herpetiformis, erythema multiforme with its many variants, epidermolysis bullosa and drug eruptions

3 All dermatologists sooner or later become impressed with the following *two facts pertaining to drug eruptions* (1) *these reactions can simulate* almost the entire gamut of the "primary" cutaneous disorders and (2) there is frequently a wide diversity of dermadromes that any one agent is capable of producing For example, the spectrum of eruptions that have been encountered include lesions simulating erythema multiforme (penicillin), psoriasis (the sulfonamides) pityriasis rosea (the barbiturates), acne (iodides), the exanthemata (penicillin) erythema nodosum (iodides the sulfonamides), lichen planus (Atabrine) the granulomata (iodides bromides), seborrheic dermatitis (gold) pemphigus (the sulfonamides), disseminated lupus erythematosus (Apresoline) and tumors of the skin (arsenic)

In view of their considerable diagnostic value a number of dermadromes will be briefly reviewed here and cross referenced with a series of accompanying photographs This chapter has been accordingly divided into the following three sections

1 Dermal Clues to Systemic Disease
2 Systemic Diseases and Their Associated Dermadromes
3 A Pictorial Atlas of Systemic Dermadromes

In general only the important dermadromes or those with some authoritative support in the literature are included Cutaneous manifestations of such infrequence as to suggest coincidental occurrence have for the most part been excluded It should be appreciated that certain skin lesions may be associated with several systemic diseases a consideration which necessitates the repeated reference to these particular entities

The illustrations included in the Atlas were selected from a large number of photographs all of which could not be included because of the limitations necessarily imposed by space They were carefully chosen to depict some well recognized relationship to systemic disorders Particular emphasis was directed to those entities that are not generally familiar to clinicians outside of dermatologic realms A number of interesting disorders that are discussed in this chapter as primarily dermatologic conditions with some general medical interest are not illustrated here They include, for example, urticaria pigmentosa Shamberg's progressive pigmentary dermatosis xeroderma pigmentosa incontinentia pigmenti, and the Vogt Koyanagi syndrome These conditions are usually adequately depicted in most dermatologic texts It was also necessary to omit a number of impor

tant dermatologic manifestations—such as carotenemia, polycythemia urticaria, spoon nails, palmar erythema, Beau's lines in the nails, xanthelasma, follicular keratosis, geographic tongue, the Raynaud phenomenon trophic ulcers, the exanthemata in many infections, myxedema, petechiae in endocarditis, radiodermatitis, severe miliaria, chloasma, and argyria—on the presumption that they are sufficiently well known to most clinicians of experience

The reader is also referred to Section X (Exfoliative Cytology) and Section XI (Biopsies in Clinical Medicine) of Part II, wherein the value and some of the pitfalls of dermal pathology are briefly reviewed

DERMAL CLUES TO SYSTEMIC DISEASE

Pigmentations and Color Changes

Although pigmentary and color changes in the skin are fairly easy to detect, they are difficult to interpret in terms of systemic disease Increased deposition of various pigments (viz, melanin, hemosiderin, carotene, and divers metals) occurs under a wide variety of circumstances such as the excoriation of pruritic areas, adrenocortical and other endocrine dysfunctions, irritation of the abdominal sympathetics, other neural influences nutritional deficiencies and the avitaminoses, drug therapy, and exposure to chemical agents sunlight, or x rays The endocrine control of melanin pigmentation was recently reviewed by Deutsch and Mescon[1405] Increased pigmentation is often seen at the site of earlier erythematous eruptions and ulcerations

In general, *the leukodermas* are not usually linked with specific systemic diseases unless those associated with syphilis, leprosy, or pinta are so regarded (The term leukoderma is most often used to designate an acquired loss of cutaneous melanin pigment) The cause is often demonstrable, as with the exposure to certain substances in industry, and following various inflammatory processes of the skin Depigmentation has resulted from hypopituitarism, the administration of various drugs (most notably BAL and thiouracil), mercuric and other metallic preparations, and occupational contact (particularly the rubber antioxidants containing the monobenzyl ether of hydroquinone)[1]

In those instances of very extensive *vitiligo* wherein the remaining normal skin actually appears to be hyperpigmented the correct diagnosis can be made by bearing in mind that the vitiliginous lesion is characterized by a convex edge The familial diathesis, the importance of emotional factors, and the possible relationship of autonomic nervous system dysfunction to the pathogenesis of vitiligo are spheres that will unquestionably be explored to advantage in the coming years

Reference is made here to the *Vogt Koyanagi syndrome* the cause of which has not yet been fathomed Its components include leukoderma, depigmentation of the hair, a bilateral uveitis (possibly further complicated by glaucoma), and auditory disturbances (tinnitus deafness) The disorder may be acute in adults, but tends to undergo a spontaneous remission after several months

Melanosis

It would be well to first consider the following brief listing of the systemic causes of melanosis (the deposition of abnormal quantities of melanin, primarily in the skin) when confronted with an extensive cutaneous discoloration[15, 1387] Reference has already been made in the preceding text to this abnormal pigmentation in most of these diseases

Melanoblasts normal in number
- Vitamin deficiencies (pellagra sprue vitamin A deficiency)
- Cirrhosis of the liver
- Blood dyscrasias (particularly Hodgkin s disease)
- Pregnancy (chloasma)
- Acanthosis nigricans
- Ochronosis
- Scleroderma
- Arsenic intoxication
- Intestinal lipodystrophy (Whipple s disease)
- Hyperthyroidism

Melanoblasts increased in number
- Pigmented nevus
- Neurofibromatosis
- Albright s syndrome (polyostotic fibrous dysplasia)
- Mucocutaneous melanosis with intestinal polyposis
- The melanotic neoplasms

Contrary to common belief, the cutaneous pigmentation in *malignant melanoma* is not brown, but a diffuse blue gray (due to its greater depth in the skin and the attendant light scattering phenomenon) Melanuria is found only in cases of melanotic carcinoma exhibiting extensive metastases It must be distinguished from the dark urine produced by porphyrinuria, alkaptonuria, myoglobinuria and hemoglobinuria The potential elusiveness of this malignancy was discussed earlier (p 328)

A diffuse or localized *melanoderma* of varying intensity (but sparing the mucous membranes) is more likely to occur in Hodgkin s disease than in the other diseases of the leukemia lymphoma group Visceral malignancy should also be suspected (*vide infra*)

Other types of intense hyperpigmentations are encountered in internal malignancies One of these, *acanthosis nigricans* (Figure 1B), consists of gray to black, papillomatous hyperkeratotic and verrucous plaques with diffuse edges and a predilection for the body folds It may also involve the mucous membranes The pigmentation has been likened to a powdering of the part with coal dust This condition is practically pathognomonic of abdominal mammary or thoracic adenocarcinomas of high malignancy only rarely have patients past puberty with this dermadrome survived

It is emphasized that the skin *per se* of the individual with acanthosis nigricans never undergoes malignant degeneration Neither the clinical nor the histopathologic features of acanthosis nigricans are helpful in distinguishing the benign and malignant types While this neoplastic dermadrome usually manifests itself about the same time as does the underlying neoplasm it is important to be aware of the fact that the dermatosis can precede or follow the latter by a considerable period of time Acanthosis nigricans should not be confused with the intertriginous changes that take place in the axillae and groins of obese individuals

When this dermatosis occurs at or before puberty, however, it is not usually associated with malignancy (Figure 1A)[1018] Juvenile acanthosis nigricans may be associated with hypogonadism and other hormonal disturbances

Another pigmentary anomaly that is almost diagnostic of *extensive intestinal polyposis* consists of the *melanin spots* on the (lower) lips (Figure 2), the fingers and toes, and the confluent blotches in the oral mucosa These specks and spots vary in color from light brown to blue-black they are usually much darker than freckles Adenocarcinomatous degeneration of the polyps in the small bowel poses a threat to these individuals (although its frequency is still disputed)[1250 1252] The syndrome is frequently inherited Either the pigmentation or the polyposis can occur independently (Also see Group XIV, p 424) Similar melanin deposits have also been seen in patients with gastrojejunocolic fistula, tuberculous ileitis, and celiac disease

The importance of not confusing the benign entity of *lipomelanic reticulosis* with Hodgkin's disease and other serious disorders was pointed out under Group VI (p 185) This syndrome is characterized by a chronic pruritic dermatosis, enlargement of the lymph nodes, generalized pigmentation or depigmentation, and eosinophilia These features and the confusing histologic picture (which includes the presence of considerable melanin pigment) have led to the erroneous diagnosis of melanocarcinoma in several instances[670]

A generalized, but variable, light brown to brownish black *melanotic* darkening of the skin occurs in *Addison's disease* The first sign of this disease may be the accentuated darkening of normally pigmented sites, pressure areas, creases, folds, and scars (Figures 55 and 56) Pale, vitiliginous areas can also develop (pp 13 and 532)

It is well to bear in mind that pigmentation may be the initial or only manifestation of a partially compensated adrenocortical insufficiency, even when the basal levels of the urinary 17-hydroxycorticoid excretion are normal[1415]

Among the pigmentations of probable endocrinal origin is included *chloasma of pregnancy* This condition consists of variously sized light brown to deep brown black melanotic macules, especially on the face and chest, but also affecting the areolae and the external genitalia They are sometimes erroneously referred to as 'liver spots" This is a frequent dermadrome in pituitary thyroid, adrenal, and ovarian disorders It has also been observed in the lymphoblastomata, cachectic states, Albright's syndrome, and Rothmund's syndrome[15]

In addition to the lymphomas and the leukemias, a number of hematopoietic disorders at times exhibit significant cutaneous pigmentations The lemon tinted, pallid, and atrophic skin is a frequent accompaniment of *pernicious anemia* (Figure 3), whereas actual pallor tends to be more striking with the hypochromic and "secondary" anemias *Jaundice* can be associated with biliary disease, hemolytic anemia, and other disorders (See Group III, pp 87 to 91) A generalized bluish red discoloration, especially about the face and fingertips is often the first clue to *polycythemia vera* (pp 188 and 540)

(*Text continues on page 515—following "Atlas"*)

AN ATLAS OF

SYSTEMIC

DERMADROMES

I Pigmentations

(Curtis Scope vol 4 1956 Upjohn)

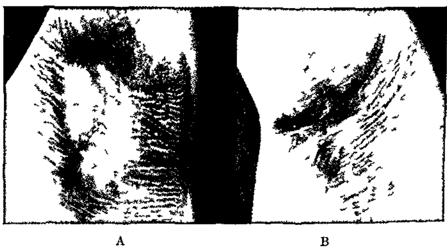


Fig 1 ACANTHOSIS NIGRICANS

The deeply pigmented verrucous papillomatous plaques of acanthosis nigricans often portend internal cancer predominantly abdominal or thoracic (The patient on the right had an abdominal malignancy) This dermadrome usually develops in adults in the intertriginous areas the nipples the umbilicus the palms or soles and sometimes on the mucous membranes Benign acanthosis nigricans unrelated to cancer most often occurs before or during puberty This was the case in the patient on the left

Fig 2 THE PEUTZ-JEGHERS SYNDROME

Light brown to dark blue-black circumoral melanin spots occur so often in intestinal polyposis as to be almost pathognomonic They appear most frequently on the lower lip and as blotches on the buccal mucosa



(Bartholomew et al Gastroenterology vol 30 195̄7)



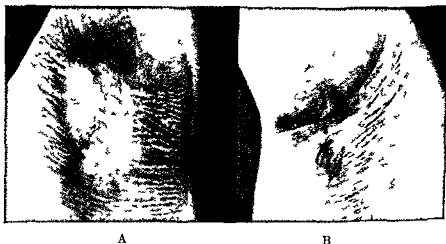
(Leopold Physical Diagnosis)

Fig 3 PERNICIOUS ANEMIA

Along with the unique pallor a yellowish waxy soft skin is characteristic of pernicious anemia A pallid atrophic skin with areas of pellagroid pigmentation (reminiscent of Addison s disease) is also suggestive of pernicious anemia

I Pigmentations

(Curtis Scope vol 4 1956 Upjohn)



A B

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(Bartholomew et al Gastroenterolog} vol 30 19ɔ")

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II The Erythemas and Purpuras

(Courtesy of Dr W B Hurlbut)

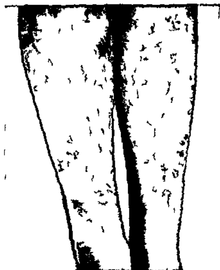


Fig 4 STEVENS-JOHNSON SYNDROME

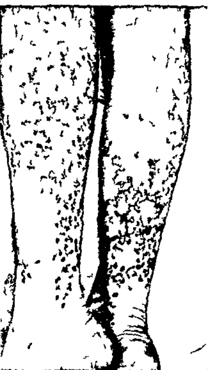
This is a very severe variant of erythema multiforme exudativum It is manifested by extensive ulcerative lesions involving many mucous membranes These include a conjunctivitis stomatitis rhinitis and urethritis High fever prostration and a papular or vesiculobullous eruption over the body also occur This unusual patient was photographed during his fourth attack he recovered shortly after the institution of cortisone therapy

Fig 5 ERYTHEMA NODOSUM

...aracteristically the erythema nodosum lesion ...nsists of a few recurrent (over three to six ...eks) acutely painful pink to red and later ...se-like raised cutaneous and subcutaneous ...dules over the tibiae They occasionally also ...velop on the arms or face Although non pecific ...s dermatosis may be the initial important clue ... a drug reaction or a variety of infections— ...ost often halogen ingestion tuberculosis or ...eumatic fever



(Pillsbury et al Dermatology)



...Wintrobe Clinical Hematology Lea and ...ebiger)

Fig 6 THE HENOCH SCHONLEIN SYNDROME

The allergic purpura in the Henoch Schonlein syndrom is nonthrombocytopenic It commonly follows an acute infection by one or two weeks and usually occurs as a symmetric dermatosis over the extensor surfaces of the lower extremities and buttocks Other components of this syndrome include urticaria joint involvement (especially of the knees and ankles) gastrointestinal bleeding and nephritis

(Sjoerdsma et al A M A Archives of Internal Medicine vol 99 1957)

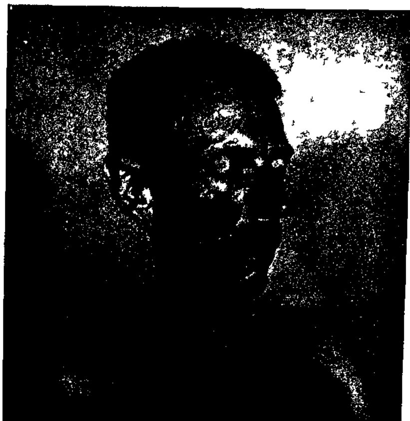


Fig 7 METASTATIC CARCINOID TUMOR OF THE SMALL BOWEL
This patient demonstrates the typical flushing and persistent cyanosis resulting from the vasomotor disturbances in this unique disorder These changes and several of the other components of this syndrome (viz intestinal hypermotility bronchoconstriction) are presumably related to the secretion of serotonin by the tumor cells

Fig 8 SYMPTOMATIC ERYTHEMA MULTIFORME

The bullous le ions predominate in this patient with erythema multiforme who had an underlying carcinoma of the colon The characteristic iris-type lesions on the forearms and extensor surfaces are not apparent in the illustration This dermadrome has also been associated with a wide variety of disorders including drug toxicity ulcerative colitis radiation therapy and a number of bacterial and parasitic infections



(Pillsbury et al Dermatology)



(Behrman Dermatolog c Clues to Int rnal Disease Grune and Stratton)

Fig 9 ERYTHEMA ANNULARE CENTRIFUGUM (MARGINATUM)

These discrete erythematous lesions begin as macular rings—most often on the chest and upper abdomen They then merge into larger confluent eruptions especially in the more severe cases of rheumatic fever This derma tosis (actually one of the variants of erythema multiforme) may either precede the attack or it may represent an important evidence of continued activ ity of the process Other dermadromes associated with rheumatic fever include erythema nodosum rheumatic nodules (Fig 21) and petechiae (even in the absence of an endocarditis)

III Xanthomatous Lesions

(Downing Cutaneous Manifestations of Systemic Diseases Charles C Thomas Springfield 1954)



Fig 10 XANTHOMA TUBEROSUM

The lesions of this metabolic disorder occur as raised firm and even pedunculated tumors They have a predilection for the extensor surfaces of the elbows and knees the palms the soles and the tendon sheaths This condition may represent the principal clinical manifestation of hereditary hypercholesterolemia or it may be found in association with diabetes mellitus hypothyroidism and severe atherosclerotic disorders affecting the heart and brain

(Duncan Diseases of Metabolism)



Fig 11 XANTHOMA DIABETICORUM (ERUPTIVUM)

This eruption occurs infrequently in diabetics usually when the disease is severe and uncontrolled The lesions are small slightly raised purplish red and have yellow centers Although they resemble pustules the lesions are solid and contain no pus The eruption exhibits some predilection for the palms soles and extensor surfaces of the extremities It usually disappears once the underlying diabetes with its associated hyperlipemia has been controlled

Fig 12 NECROBIOSIS LIPOIDICA DIABETICORUM

The sharply defined red to brown plaques of this dermadrome typically appear over the anterior surfaces of the legs They can antedate the discovery of the underlying diabetes mellitus by a considerable period There is a violaceous halo and a telangiectatic atrophic or necrotic center The lesions may disappear once the diabetes is controlled Women are predominantly affected



(Lewis Practical Dermatology)



(Courtesy of Dr C W Lane)

Fig 13 THE HAND SCHÜLLER CHRISTIAN SYNDROME

This patient demonstrates several classic features of this generalized normocholesterolemic xanthomatous process These consist of the diffuse brownish red papular eruption over the chest and abdomen the exophthalmos and the bulging forehead Other components include diabetes insipidus a hemorrhagic eruption and ulcerated granulomatous lesions of the mucocutaneous areas



(Pillsbury et al Dermatology)

Fig 14 LETTERER SIWE DISEASE
This infant exhibits the hepatosplenomegaly and the cutaneous components that characterize this acute nonlipid disseminated reticuloendotheliosis The dermatosis includes purpura petechiae and a seborrheic type of eruption

IV *The Photodermatoses*

(Behrman Dermatologic Clues to Internal Disease Grune and Stratton)



Fig 15 HYDROA AESTIVALE
The presence of this eruption following exposure to sunlight in a young patient (especially boys) should suggest the possibility of congenital porphyria Note the *dermatosis over the* exposed areas of the face and extremities stemming from the photosensitization In the more severe recurring cases these vesicular and bullous lesions are accompanied by scarring deformities and corneal scarring

Fig 16 CONGENITAL PORPHYRIA (ERYTHRODONTIA)

The finding of a pink to brown discoloration of the teeth suggests the presence of porphyria congenita erythropoietica This phenomenon actually begins *in utero* Marked sensitivity with diffuse pigmentation sclerodermoid changes and extensive bullae formation are due to the sensitizing porphyrins There may also be hirsutism in these individuals



(Curtis Scope vol 4 1956 Upjohn)



(Watson in Duncan Diseases of Metabolism)

Fig 17 MIXED PORPHYRIA

This patient demonstrates the purplish brown pigmentation of the skin along with the characteristic discoloration of the urine after it has been allowed to stand for some time Evidence of liver dysfunction can usually be found (this patient also had moderate ascites) Abdominal pain and neurologic symptoms are often striking but true photosensitivity is infrequent here

V Herpes and Herpetiform Lesions

Fig 18 HERPES ZOSTER GENERALIZATA

In addition to the bandlike zone representing the original eruption this patient also exhibits a generalized varicelliform dissemination of her infection The occurrence of such severe herpes zoster with hemorrhagic necrotic or bullous components should suggest the possibility of an underlying lymphatic leukemia or myeloma Unexplained herpes zoster should also direct attention to other systemic disorders particularly Hodgkin s disease internal malignancies and drug reactions



(Lewis Practical Dermatology)



Fig 19 KAPOSI S VARICELLIFORM ERUPTION

This severe eruption represents an infection caused by the virus of herpes simplex It is apt to be encountered most often in young children with atopic dermatitis The umbilicated varicelliform lesions tend to involve the head neck and upper trunk Histologic study may be necessary to distinguish it from vaccinia especially if there is neither a history of vaccination nor exposure to recently vaccinated individuals

(Barton and Brunsting Archives of Dermatology and Syphilology)



(Courtesy of Drs J B and Bedford Shelmire)

Fig 20 DERMATITIS HERPETIFORMIS

These intensely pruritic papulovesicles on erythematous bases can occur in a chronic form of undetermined cause (Duhring s disease) or they may be associated with necrotic malignant tumors cirrhosis of the liver radiation therapy and drug poisoning Regression of the dermadrome has been observed following treatment of an underlying neoplasm

VI Tumors and Nodules

(Major and Delp Phys cal Diagnosis)



Fig 21 RHEUMATIC FEVER (NODULES)

The finding of these subcutaneous nodules near the joints and tendons on the hands wrists ears face scalp and other areas may be of considerable aid in the diagnosis of rheumatic fever These lesions are usually nontender dusky red (although the overlying skin appears normal) and partially fixed to the deep fascia tendons or periosteum. They tend to disappear after several weeks

(Downing Cutaneous Manifestations of Systemic Diseases Charles C Thomas Springfield 1954)



Fig 22 LATE SYPHILIS (JUXTA ARTICULAR NODES)

These tumors probably represent a unique fibroid type of gumma They are often so firm as to suggest an osteoma They may be cutaneous or subcutaneous and typically occur near the extensor surfaces of the joints The area over the olecranon process (as shown in this patient) is typical

(Kierland Geriatrics vol 12 1957)



Fig 23 KAPOSI S SARCOMA

This unique angiosarcoma is characterized by pigmented hemorrhagic plaques and nodules on the lower extremities as illustrated in this patient There is often a history of long standing lymphedema The rubbery nodules have a tendency to coalesce The possibility of other concomitant sarcomatous tumors in the viscera should be raised whenever this lesion is diagnosed

(Kierland Geriatrics vol 12 1957)



Fig 24 METASTATIC CARCINOMA TO THE SKIN

The finding of recent cutaneous and subcutaneous tumor in a patient with a puzzling illness may be the first conclusive clue to the presence of an internal malignancy The lesions may be single or multiple and offer diagnostic material for biopsy They are occasionally limited to the scalp

(Kierland Medical Clinics of North America July 1956)



Fig 25 LYMPHATIC LEUKEMIA

Patches of leukemia cutis are specific infiltrations of the skin They vary in size and shape and can ulcerate extensively with the formation of refractory ulcers Residual scars may become the sites of such infiltration The patient shown in this photograph had lymphatic leukemia with infiltrated leukemic plaques Widespread specific nodules and cutaneous tumor are also frequent dermal reflections of systemic involvement in the leukemic lymphomatous group of diseases The lesions are usually soft vary from reddish to dark brown and may become quite large

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Fig 26 HODGKIN S DISEASE

(See illustrations on opposite page)

The pathologically specific dermadromes of Hodgkin s disease and lymphosarcoma are not common in contrast to the nonspecific manifestations resulting from the intense pruritus (prurigo lymphatica) (Fig 26B) They can occur as scattered individual tumors of various sizes and *colors which may or may* not ulcerate (Fig 26A) or as grouped nodules which form plaques Either of these disorders might also be initiated clinically as an *exfoliative erythroderma* ('l homme rouge')



Fig 26 HODGKIN'S DISEASE

(See opposite page for legend.)

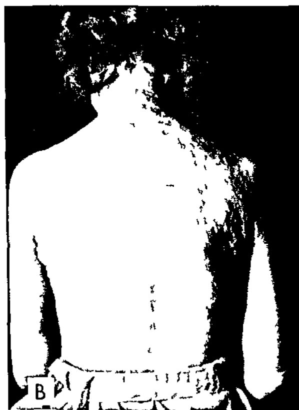


Fig 26 HODGKIN'S DISEASE

(See opposite page for legend.)

(Kierland Medical Clinics of North America July 1956)



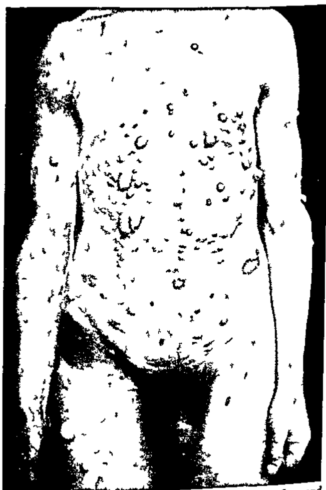
(I illsbury et al Dermatology)

Fig 27 SARCOIDOSIS

The clinical recognition and histologic study of small tumors have proved to be of considerable value in diagnosing a number of obscure syndromes caused by sarcoidosis The lesions rarely ulcerate They tend to occur in groups or as infiltrated plaques on the face arms and shoulders Enlargement of the lacrimal and parotid glands offers another clue to the presence of this disease

Fig 28 NEUROFIBROMATOSIS

The characteristic benign tumors and café au lait spots are classically shown in this patient Only the latter may be present in certain formes frustes however The relationship of von Recklinghausen s disease to epilepsy bone lesions and pheochromocytoma is cited in the text



(Ormsby and Montgomery Diseases of the Skin Lea and Febiger)

Fig 29 MONOCYTIC LEUKEMIA
Granulomatous swollen gums and other painful hemorrhagic and necrotic lesions of the oral nasal pharyngeal or ocular mucous membranes accompany a high percentage of the leukemias This is particularly true of the monocytic type as illustrated by this patient



(Thoma and Robinson Oral and Dental Diagnosis)

VII Nail Changes

(White Ciba Clinical Symposia vol 2 1950)



Fig 30 HYPOPARATHYROIDISM
The nail atrophy and the psoriasis-like erosions of the nail plates are frequent dermadromes in parathyroid insufficiency They are presumably related to the disturbed metabolism of calcium and other elements This patient also had a dry scaly skin with widespread pigmented lesions and scanty hair

(White Ciba Clinical Symposia vol 2 1950)



Fig 31 HYPERTHYROIDISM

Although not frequently seen in as striking a manner as in this colored hyperthyroid patient the longitudinal ridging brittleness and atrophy of the nails with loosening of their distal ends (*onycholysis*) is *characteristic* Similar changes and spoon nails are also encountered as dermadromes of hypothyroidism

(Downing Cutaneous Manifestations of Systemic Diseases Charles C Thomas Springfield 1954)

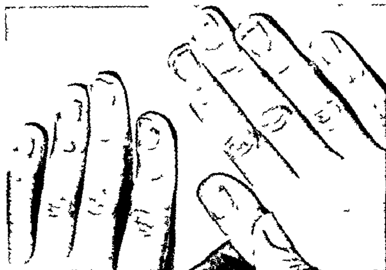


Fig 32 TRICHINOSIS

The subungual splinter hemorrhages encountered in this patient with trichinosis are classic. Their presence may also be of considerable diagnostic importance in patients suspected of having an endocarditis

VIII Tongue Changes

Fig 33 LATE SYPHILIS

The clinician should promptly suspect lues in patients who exhibit leukoplakia and interstitial glossitis as was the case in the patient here photographed The precancerous nature of these tongue changes is generally accepted



(Pillsbury et al Dermatology)

(White Ciba Clinical Symposia vol 2 1950)



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IX Intoxications and Allergies

Fig 36 BROMODERMA SIMULATING LATE SYPHILIS

The lessened use of the halogens in therapy has reduced clinicians awareness of the distinctive granulomatous vegetating tumors caused by bromides and iodides The lesions in both bromoderma and iododerma tend to localize about the sebaceous glands as painful nodular or pustular eruptions that may simulate ordinary acne Unlike acne however there is an absence of comedones in bromoderma



(Becker and Obermayer Modern Dermatology and Syphilology J B Lippincott)



(Lewis Practical Dermatology)

Fig 37 ARSENICAL DERMATOSIS

Wartlike pale yellow to brownish keratoses—especially over calluses on the palms and soles—are frequent dermal clues to chronic arsenic poisoning They appear relatively early in the course of chronic exposure to arsenic This may be incurred by the ingestion of Fowler's solution or the prolonged exposure to arsenic containing insecticides Malignant epitheliomas frequently complicate these keratoses



(Leopold 1 hysical Diagnosis)

Fig 34 CLUBBI\G OF THF NAILS

In chronic pulmonary diseases such as bronchiec tasis lung abscess and hemangiomas the distal phalanges often become broadened with the nails enlarged overhanging and increasingly convex Heart disease also causes this deformity particularly in the case of certain congenital disorders associated with cyanosis and polycythemia and in subacute bacterial endocarditis If recent pulmonary and mediastinal neoplasms must be suspected

Fig 35 PRIMARY SYSTEMIC AMYLOIDOSIS

Progressive macroglossia was one of the most characteristic features in this patient with systemic amyloidosis (the tongue finally becoming twice its normal size) As the disorder progressed the small trans lucent papules and localized purpuric spots were followed by the development of large deep furrows denudation and a subsequent pyogenic membrane caused by the trauma He was also found to have a nodular infiltration in the eyelids



(Courtesy of Dr F W Lynch)

X Vascular Lesions

(Gresham and Phear American Journal of Medicine October 195")



Fig 40 GANGRENE OF THE FINGERS IN POLYARTERITIS

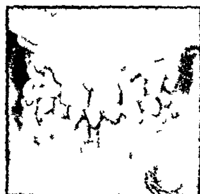
This thirty-one year old patient experienced a progressively severe Raynaud s phenomenon for several months prior to the onset of the gangrene Therapy with steroids nerve blocks and and intra-arterial Priscoline was of little value The diagnosis of periarteritis nodosa was made histologically after necropsy The Raynaud phenomenon is observed more commonly in disseminated lupus erythematosus and other systemic disorders presumably due to the relative infrequency of polyarteritis

(Allen Barker and Hines Peripheral Vascular Diseases)



Fig 41 HEREDITARY HEMORRHAGIC TELANGIECTASIA

The distribution of the telangiectases on the face lips and mucous membranes in this patient is typical Small hemangiomatous papules can also be found The recognition of these dermal clues in the presence of unexplained bleeding from the respiratory genitourinary or gastrointestinal tracts is often diagnostic



(Thoma and Robinson Oral and Dental Diagnosis)

Fig 38 LEAD POISONING

The presence of a dark lead line at the gingival margin (halo saturnis) is suggestive but *not* diagnostic of this disorder Other forms of metallic poisoning may initiate or contribute to a gingivitis with subsequent pigmentation of the gums These metals include bismuth gold mercury, and silver

Fig 39 VITAMIN A INTOXICATION

The hypervitaminosis A in this patient was caused by the prolonged and excessive ingestion of oleum percomorphum Tender and symmetric swellings over the fifth metatarsals and over the right tibia can be seen The other grossly apparent features of the intoxication she exhibited were excessive dryness and cracking of the lips and tender hyperostoses in the occipital region and on both forearms



(Caffey American Journal of Roentgenology Radium Therapy and Nuclear Medicine vol 61 1951)

(Shi k and Kvale n Allen Barker and Hines Peripheral Vascular Di eas s)

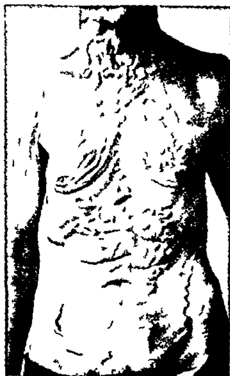


Fig 44 TEMPORAL ARTERITIS

This condition is characterized by the pre ence of exquisitely painful tender and thickened superficial temporal arteries as illustrated in this patient It is important to recognize because of the frequent concomitant occurrence of a similar panarteritis involving the retinal and visceral arteries for which steroid therapy may be beneficial

Fig 45 VENA CAVAL OBSTRUCTION

Dilatation of the veins over the chest with or without edema and cyanosis of the face and upper limbs may be an important and early objective manifestation of invasion and occlusion of the superior vena cava by a primary or metastatic mediastinal malignancy a lymphoma or a bronchogenic carcinoma The superior vena caval yndrome can also re ult from an aortic aneur ysm spontaneous thrombosis and chronic fibrous mediastinitis due to various causes The direction of blood flow is normal if the obstruction is above the azygus orifice but reversed if this channel is involved



(Leopold Physical Diagnosis)



(Allen Barker and Hines Peripheral Vascular Diseases)

Fig 42 THROMBOANGIITIS OBLITERANS (SUPERFICIAL THROMBOPHLEBITIS)

Concomitant involvement of the coronary cerebral renal and mesenteric vessels may accompany the peripheral phlebitis and arterial occlusive process in Buerger s disease The relative rarity of this disorder nowadays however should make the clinician consider other causes for a spontaneous and recurrent thrombophlebitis In this regard particular attention is directed to the neoplasms the collagen disorders and polycythemia vera

Fig 43 ANGIOKERATOMA CORPORIS DIFFUSUM UNIVERSALE

The lesions in this unusual disorder consist of small raised and partially hyperkeratotic vascular aneurysms These angiokeratomas were not only prominent on the chest and abdomen in this patient but also over the buttocks and scrotum The condition is of twofold medical interest because it can be confused with hereditary telangiectasia and the various purpuras and because of the many clinical pictures that might result from the visceral involvement



(Fessas et al A M A Archives of Internal Medicine vol 95 1955)

(McCombs Internal Medicine Year Book)

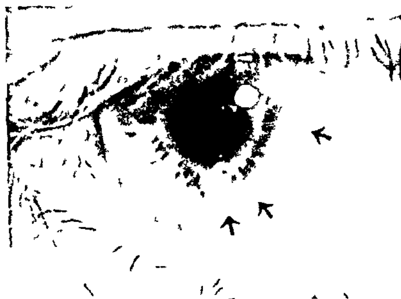


Fig 47 HYPERCALCEMIA

This patient had a long standing peptic ulcer for which he ingested excessive amounts of milk and alkali The ocular calcification illustrated is in the form of a band keratopathy It might be readily mistaken for arcus senilis by the naked eye Note the clear rim adjacent to the sclera which aids in this differentiation The importance of this sign is enhanced by the fact that it could represent the only definite evidence of a previous hypercalcemia if the serum calcium normalizes because of secondary renal damage

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Fig 46 PELLAGRA (CAUSED BY THERAPEUTIC DIET)

(*See illustration on opposite page*)

This patient is a thirty eight year old well to do hypertensive who was placed on a strict diet for both elevated blood pressure and obesity to which she rigidly adhered for five years She then developed the characteristic eruption of pellagra over the dorsa of the hands and the exposed areas of the forearms Other pellagrins also exhibit a similar erythematous dermatitis over the face the neck and as a collarette extending *onto the upper sternal region* The eruption stems from the associated photosensitivity

XI Metabolic-Nutritional Disorders

(Spies Postgraduate Medicine vol 17 195)

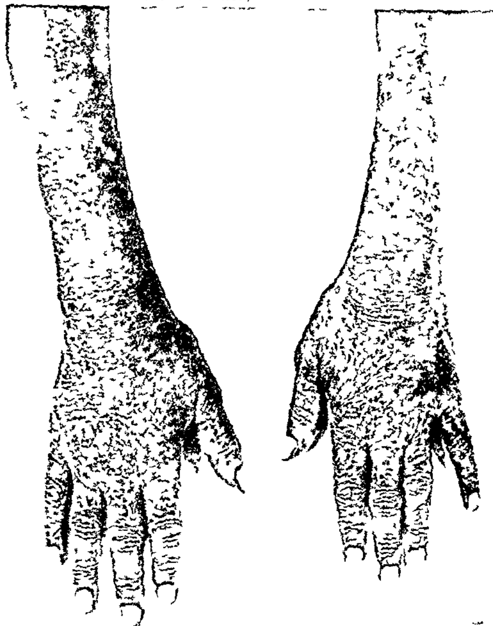


Fig 46 PELLAGRA (CAUSED BY THERAPEUTIC DIET)

(See opposite page for legend)

(Courtesy of Dr James W Smith)



Fig 49 ALCAPTONURIC OCHRONOSIS

The patches of light brown pigment in the sclerae on either side of the corneal limbus are demonstrated by this patient Other dermadromes in this disorder include a butterfly-shaped brown pigmentation of the facial skin pigmentation of the ear cartilage and a bluish discoloration of the knuckles resulting from the pigmentation of the underlying tendons

Fig 50 CALCINOSIS CUTIS

The cutaneous and subcutaneous deposition of calcium occurs in the form of plaques and tumors of various sizes around the larger joints They are sharply circumscribed and are at times accompanied by erythematous macules Ulcerations of the lesions can take place with the discharge of calcifi masses This disorder may be a manifestation of local disuse atrophy or it might be an important dermadrome in the hypercalcemic states scleroderma dermatomyositis poikiloderma and acrodermatitis chronica atrophicans



(Lewis Practical Dermatology)

(Courtesy of Eli Lilly and Co)

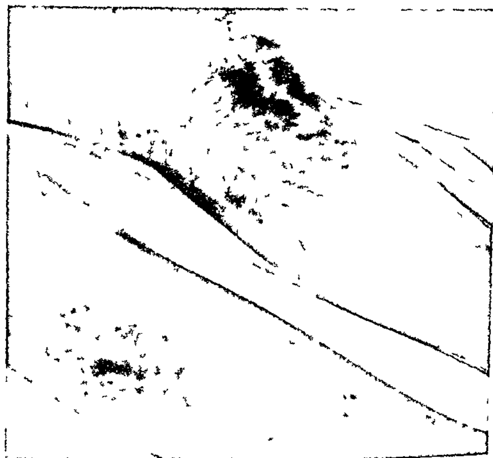


Fig 48 ADULT SCURVY

Scurvy is fortunately not observed very often at the present time either in infants or adults It must be kept in mind however not only in alcoholics and in individuals who cannot obtain adequate nourishment but also in bachelors psychiatric patients and in chronically ill patients with restricted diets who develop ecchymoses spongy bleeding gums and perifollicular hemorrhages

XII The Endocrinopathies

(Zugerman New England Journal of Medicine vol 251 1954)



Fig 53 CIRCUMSCRIBED PRETIBIAL MYXEDEMA

The pretibial lesions in this patient became manifest several months after he was treated for an exophthalmic goiter and hyperthyroidism with antithyroid medication and a thyroidectomy They typically appear as nontender nonpitting yellowish to reddish brown plaques or nodules with a cartilagenous consistency Considerable variation in the size shape and color is often encountered



(Bauer and Klemperer in Duncan Diseases of Metabolism)

Fig 51 GOUT

Tophaceous depo its may be found not only on the ears but also as hard nontender nodules at the juxta articular sites The tophi illustrated in this patient are situated about the terminal phalangeal joint of the finger As they subsequently increased the overlying skin ulcerated discharging the accumulated urate depo its

Fig 52 HEMOCHROMATOSIS (COMPARED WITH NORMAL)

The generalized melanoderma in pigmentary cirrhosis can vary in color from light bronze to deep brown black or slate-blue It tends to be most pronounced in the axillae the genital regions the nipples scars and areas exposed to light Pigmentation of the mucous membranes alopecia and pruritus may also be present



(Major and Delp Physical Diagnosis)

XII The Endocrinopathies

(Zugerman New England Journal of Medicine vol 251 1954)



Fig 58 CIRCUMSCRIBED PRETIBIAL MYXEDEMA

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(Downing Cutaneous Manifestations of Systemic Diseases Charles C Thomas Springfield 1954)



Fig 54 KERATODERMA CLIMACTERICUM

This menopausal patient shows marked hyperkeratosis of the plantar areas A similar eruption was also present on the palms but to a much lesser degree Estrogenic therapy effected considerable improvement The exact hormonal etiology of this disorder is still not clear some dermatologists actually regarding it as a neurodermatitis or psoriasis localized to these areas

(Williams Textbook of Endocrinology)



Fig 55 ADDISON'S DISEASE

This patient demonstrates the typical addisonian pigmentation secondary to tuberculosis of the adrenal glands The color is usually tan but may vary from a slate to an intense black. It tends to be most pronounced over the exposed and normally darker skin and over pressure or friction sites The pigment in the scars above and lateral to each breast (representing the sites of previous pellet implantations) and the many black freckles and moles are also characteristic

(Downing Cutaneous Manifestations of Systemic Diseases Charles C Thomas Springfield 1954)



Fig 54 KERATODERMA CLIMACTERICUM

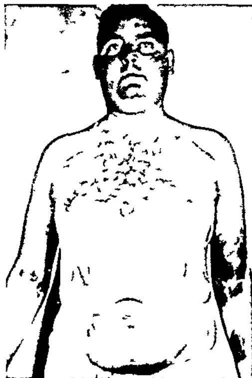
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(Soffer Diseases of the Endocrine Glands Lea and Febiger)

Fig 57 SHEEHAN S SYNDROME

The possibility of a postpartum necrosis of the anterior pituitary must be seriously entertained in women who have had difficult deliveries and then complain of asthenia and loss of sexual function. This patient demonstrates the characteristic loss of the axillary and pubic hair and the fact that there need be little associated weight loss Other dermal features in the anterior pituitary hypofunction syndromes include the pale yellow thin and smooth skin dystrophy of the nails and at times a myxedematous facies due to the secondary hypothyroidism.



(Harrison and Laidlaw Surgical Forum 1953)

Fig 58 THE CUSHING SYNDROME

This thirty two year old male exhibits most of the dermal features that characterize the important Cushing syndrome—in this case due to bilateral adrenal cortical hyperplasia Prominent are the profound plethora the extensive ecchymoses and easy *bruisability the permanent reddish to* purplish abdominal striae and obesity involving the face and trunk He also was found to have osteoporosis hypertension a decreased carbohydrate tolerance and an elevated excretion of urinary corticosteroids

(Hyman Integrated Practice of Medicine)



Fig 56 ADDISON S DISEASE

The melanin ink-spot pigmentation of the buccal mucosa is shown in this patient with hypoadrenalism Pigmentary changes were present in the gums at the gingival margin Similar buccal pigmentation has also been observed in certain racial groups and in other disorders (hyperthyroidism arsenical intoxication tar melanosis) It occurs very infrequently in hemochromatosis or in patients with symptomatic hypoadrenalism due to anterior pituitary hypofunction

(Williams Textbook of Endocrinology)



Fig 61 PSEUDOHYPOPARATHYROIDISM

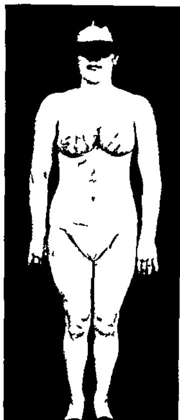
One of the characteristic features of this target organ defect is the abnormal shortness of the metacarpal and metatarsal bones This anomalous growth can be demonstrated clinically by the deficient or recessed knuckle prominence when the fist is clenched especially over metacarpals IV and V Other manifestations exhibited by this patient were a short stocky stature hypocalcemia tetanic episodes and calcification of the soft tissues

(Thoma Oral Pathology C V Mosby)



Fig 62 HYPERPARATHYROIDISM

One of the clues to a functioning parathyroid adenoma in this patient was the presence of multiple giant-cell tumors of the maxilla Calcinosis cutis is only infrequently a dermadrome in this disorder



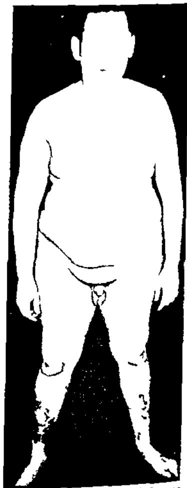
(Campbell Urology)

Fig 59 ADRENAL VIRILISM

The adrenal virilism in this twenty eight year old female stemmed from an adrenal cortical carcinoma The masculine habitus and the hirsutism of the shoulders and breasts seen here were strikingly reversed following surgical removal of the tumor (This operation also effected a return of her menses) Facial hirsutism was an added problem here but had been treated by electrolysis

Fig 60 THE KLINEFELTER SYNDROME

This twenty five year old male demonstrates the following typical features of this interesting condition gynecomastia sparse facial hair a female distribution of the pubic hair under the abdominal panniculus obesity a small penis small testes and a thin pale yellowish skin Determination of the FSH may aid in ascertaining whether this syndrome in an alcoholic patient is due to primary hypogonadism or is secondary to the impaired hepatic function



(Soffer Diseases of the Endocrine Glands Lea and Febiger)

XIII Nervous System Disorders


(Pillsbury et al Dermatology)

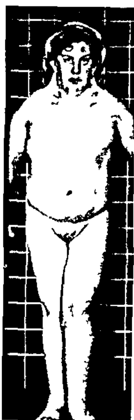
Fig 65 THE STURGE-WFBFR DIMITRI SYNDROME

This thirty five year old patient with encephalo-trigeminal angiomatosis shows a predominantly unilateral hemangioma overlying the distribution of the superior and middle branches of the right trigeminal nerve The characteristic calcification of the cerebral convolutions was also demonstrated in the occipital region by skull films


(Courtesy of Dr Franklin H Top)

Fig 66 CAVERNOUS SINUS THROMBOSIS

This patient still evidences the furuncle of the face that initiated the severe intra cranial inflammatory process Note the dusky red color of the skin the protrusion of the eyeball and the dilated veins



(Wilkins Endocrine *Disorders* Charles C Thomas Springfield 1957)

Fig 63 OVARIAN AGENESIS

This fifteen year old girl shows both the webbing and shortening of the neck and the stunted growth that are characteristic of her gonadal dysgenesis Her height age was twelve years Other manifestations include the under development of the breasts and genitalia absent or minimal axillary and pubic hair osteoporosis and many congenital anomalies

Fig 64 THE ALBRIGHT SYNDROME

This nine year old girl exhibits the following features that characterize this syndrome dark brown flat patches over the right side of the trunk the right arm and the forehead (actually noted shortly after birth) bone lesions due to the polyostotic fibrous dysplasia rapid growth commencing at the age of three years with a bone and height age of fifteen years at the age of nine first menses at the age of seven enlargement of the thyroid and adolescent development of the breasts external genitalia and hair in the axillae and pubic regions at this age



(Wilkins Endocrine Disorders Charles C Thomas Springfield 1957)

XIV The Dyscollagenoses

Fig 68 LUPUS ERYTHEMATOSUS
This patient with acute disseminated lupus erythematosus demonstrates the bilateral symmetric erysipelas like dermatitis of the face The sharply demarcated borders of the more typical butterfly pattern are not always present Other characteristic features of the dermatosis include the atrophic dilated follicles with follicular plugs involvement of the neck and exposed extremities and ulcerations in the mouth



(Pillsbury et al Dermatology)



(Lewis Practical Dermatology)

Fig 69 POLYARTERITIS
The painful crops of deep seated erythematous nodules and papules in this disease tend to occur along the course of a superficial vessel on the limbs or trunk Other dermadromes may include the Raynaud phenomenon gangrene (Fig 40) purpura petechiae and eruptions simulating erythema nodosum or erythema multiforme

(Hyman Integrated Practice of Medicine)



Fig 67 ADENOMA SEBACEUM IN TUBEROUS SCLEROSIS

The finding of these firm yellowish waxy papules over the cheeks chin and forehead in a patient with mental retardation or epilepsy should raise the possibility of tuberous sclerosis Other dermadromes in this disorder include changes in the nails subungual and periungual fibromas nevi vitiligo pigmentation and even neurofibromatosis

Fig 71 DERMATOMYOSITIS

This patient with fatal dermatomyositis shows the typical purplish discoloration and swelling of the eyelids and circumorbital area along with a symmetrical violaceous erythema that involves not only the face but also the neck and trunk *Telangiectases* pigmentation interstitial calcinosis and cutaneous lesions resembling scleroderma erythema multiforme and erythema *nodosum* also may accompany the severe tenderness and weakness of the muscles



(Courtesy of Dr Rustin McIntosh Babies Hospital)

(Vallee New England Journal of Medicine vol 235 1946)



Fig 72 SCLEREDEMA ADULTORUM

This patient exhibits the persistent brawny induration and firm nonpitting edema of the face and neck that occur in Buschke's disease The marked eyelid changes chemosis and pallor of the edema are striking The condition most often follows a *respiratory infection* but tends to be benign Neither the atrophy contractures pigmentary changes nor involvement of the hands that characterize *scleroderma* are noted here

(Downing Cutaneous Manifestations of Systemic Diseases Charles C Thomas Springfield 1954)



Fig 70 GENERALIZED SCLERODERMA

Diffuse progressive scleroderma not only involves the skin and subcutaneous tissues but also a number of visceral organs (especially the lungs heart kidneys and gastrointestinal tract) The patient with this disorder illustrated above demonstrates the atrophied hard pigmented and wrinkleless skin over the face the upper anterior chest and the upper extremities Other features of her disease include the Raynaud phenomenon telangiectasia and calcinosis

XV The Infections

Fig 75 LUPUS MILIARIS DISSEMINATUS FACIEI

These lesions represent the hematogenous dissemination of tubercle bacilli They occur as small reddish brown macules and papules especially on the face This dermadrome may be chronic but more often is found in patients with acute fulminant pulmonary or meningeal tuberculosis



(Hyman Integrated Practice of Medicine)

(Courtesy of Dr Kenneth Landauer)



Fig 76 TYPHOID FEVER

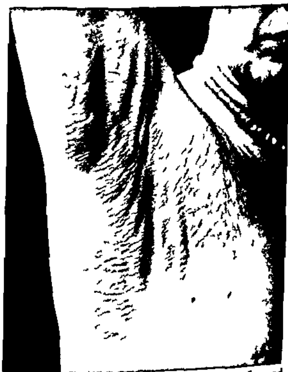
The relative infrequency with which this important infection occurs in the United States prompted the inclusion of the characteristic exanthem here illustrated It consists of small rose-red discrete maculopapules which last but a few days The abdomen is the most typical site although the rose spots may also be found on the thighs chest and back Successive crops can occur during the febrile period A similar eruption has been observed in the course of other infections (viz paratyphoid fever and trichinosis)



(Pillsbury et al Dermatology)

Fig 73 WEBER CHRISTIAN DISEASE

This patient shows the erythema of the skin overlying the raised tender and freely movable subcutaneous nodules on the thighs and legs The coalescence of the individual nodules into larger ones can also be observed Other clinical characteristics include fever and cutaneous exacerbations and remissions



(Ormsby and Montgomery Diseases of the Skin Lea and Febiger)

Fig 74 PSEUDOXANTHOMA ELASTICUM

The skin changes illustrated above may call attention to elastica disease They consist of symmetrical cream colored to orange papules in the neck and flexural folds of the axillae and long yellowish striae over these areas and at the sites of trauma These findings along with angioid streaks of the retina can be rewarding observations in puzzling cases of gastrointestinal bleeding or vascular disturbance

(Andrews Diseases of the Skin)

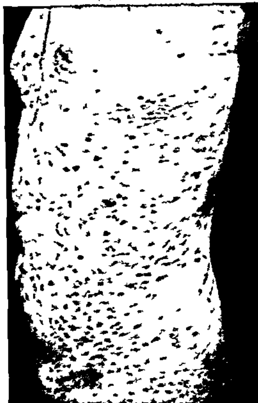


Fig 78 SYPHILIS

This patient with secondary syphilis exhibit a typical large papular syphilid reaction The individual lesions are round coppery in shade and slightly raised with a palpable deep firm infiltration They may be covered with a thick adherent scale In addition to the trunk involvement noted here this eruption characteristically is also distributed over the face the flexural surfaces of the upper and lower limbs and as dusky spots on the palms and soles

(Allen Barker and Hines Peripheral Vascular Diseases)



Fig ~~ ERYTHEMA INDURATUM

This disorder represents another tuberculous dermadrome The chronic but relatively painless nodular and ulcerative lesions of the legs—especially over the lower calf area—serve to distinguish this entity from that of erythema nodosum (in which ulceration takes place only rarely)

(Courtesy of Dr John Lamb.)



Fig 81 MONILIASIS (CANDIDIASIS)

The *cutaneous* eruption resulting from this yeastlike *fungus* may be *localized to the* hands, nails, vulva, and *intertriginous areas*, or it may be generalized with involvement of the *mouth* and intestinal tract. The *chronic paronychia, onychomycosis* and [illegible] on the glabrous skin shown in this patient are characteristic. Careful *evaluation for* a possible *underlying* diabetes mellitus *must* always be made in such instances.



(Williams Textbook of Endocrinology)

Fig 79 MENINGOCOCCEMIA
This patient had experienced the Waterhouse-Friderichsen syndrome caused by a meningococcemia of two days duration at the time she was photographed The initial macular and petechial eruption has progressed to the stage of hemorrhagic lesions with some necrosis The mucous membranes were also similarly involved

(Courtesy of Dr Stanley O Chambers)



Fig 80 KERATOSIS BLENNORRHAGICA (GONORRHEAL)
Gonorrheal keratoderma is infrequently seen nowadays The lesions are initially vesicular but then become covered with a thick horny crust They tend to be symmetrical and most numerous over the palms soles nails elbows and knees although other areas of the body may be involved Very similar eruptions have also been observed in Reiter s disease

(Conant et al Manual of Clinical Mycology)



Fig 83 ACTINOMYCOSIS

This patient shows the subcutaneous infection typical of actinomycosis with the development of progressively larger nodules and their ulceration either through the skin or to adjoining sinus tracts The characteristic (but not diagnostic) yellowish sulfur granules may be observed in the pustular discharge expressed from these lesions

(Conant et al Manual of Clinical Mycology)



Fig 82 NORTH AMERICAN BLASTOMYCOSIS

This patient manifests the multiple elevated discrete granulomatous lesions that occur over the exposed areas in this disease They are spread by autoinoculation The initial pathologic change may be a cutaneous pustule on the face hands or ears Other features of the lesions include their vascularity the thick crusts and the underlying small sinuses which connect with subcutaneous abscesses

Fig 85 TULAREMIA

This patient illustrates the more common ulceroglandular type of tularemia It developed following a tick bite of the left knee area Note the enlargement of the primary papule its breaking down with the formation of a necrotic ulcer and the tender lymphadenopathy involving the left inguinal glands which have begun to suppurate While firm subcutaneous nodules can develop along the course of the lymphatic channels both in this disease and in sporotrichosis a regional adenopathy is unusual in the latter disorder



(Courtesy of Drs Thomas B Magath and Wallace M Yater)



(Courtesy of Drs A Amoish and A E Palmer)

Fig 86 HISTOPLASMOSIS

One of the dermal manifestations in the progressive form of histoplasmosis is the development of persistent ulcerative granulomas involving the mucocutaneous areas and mucous membranes especially those of the mouth pharynx and genitalia Purpura papular eruptions and chronic abscesses occur much less frequently in this disease in association with the lymph adenopathy the hepatosplenomegaly and fever

(Courtesy of Dr M A Gifford)



Fig 84 COCCIDIOIDOMYCOSIS

This patient exhibits multiple granulomatous lesions with ulceration due to this mycosis They are deep seated and relatively painless granulomas from which a thick yellowish gray pus may be discharged The eruption might simulate blastomycosis sarcoid or tuberculosis verrucosa cutis Erythema nodosum is another important dermadrome in this infection

Fig 85 TULAREMIA

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(Lewis Practical Dermatology)



Fig 87 TRICHINOSIS

This patient shows the typical edema of the face and eyelids that accompanies the severe muscular pain and tenderness at this stage of the infestation Initially there may be some confusion with dermatomyositis Other dermadromes in this disorder include conjunctival petechiae splinter hemorrhages of the nails (Fig 32) and a maculopapular eruption over the chest or abdomen that could simulate the rose spots of typhoid fever

XVI Ulcerations



(Pillsbury et al Dermatology)

Fig 88 DIPHTHERIA

This is the appearance of a diphtheritic lesion of the skin eleven days after its onset Virulent *Corynebacterium diphtheriae* organisms were cultured Note the adherent membrane It is important to recognize cutaneous diphtheria in its many forms because of the high incidence of ensuing cardiac and neurologic complications if treatment is not promptly instituted



(Major and Delp Physical Diagnosis)

Fig 89 SICKLE CELL ANEMIA

Deep chronic punched out ulcers about the ankles are striking dermal clues in patients with sickle cell anemia These ulcerations have also been observed in patients with hereditary hemolytic anemia and with Cooley s anemia

(Lewis Practical Dermatology)



Fig 87 TRICHINOSIS

This patient shows the typical edema of the face and eyelids that accompanies the severe muscular pain and tenderness at this stage of the infestation Initially there may be some confusion with *dermatomyositis* Other dermadromes in this disorder include conjunctival petechiae splinter hemorrhages of the nails (Fig 32) and a maculopapular eruption over the chest or abdomen that could simulate *the rose spots of* typhoid fever

(Courtesy of Dr G M MacKee)



Fig 91 CONGENITAL ECTODERMAL DEFECT

This patient shows the sequelae of incomplete development of the epidermis and it appendages They consist of the sparse scalp hair the high and wide cheek bones the depressed bridge of the nose the scanty eyebrows 'pseudorhagades at the buccal commissures thickened lips and the presence of small papules and telangiectases The appearance of these individuals might be confused with that of congenital syphilis or mongolism Other features include the absence of sweat and sebaceous glands absence of the mammary glands dental aplasia and absence or malformation of the nails

XVII Miscellaneous



(Baer Brennemann s Practice of Pediatrics vol 4 W F Prior)

Fig 90 ARACHNODACTYLY

A number of features typical of this disorder can be observed in this twelve year old girl with Marfan s syndrome These include the long extremities the slender trunk and face spider hands and feet with long fingers and toes and lax joints with genu valgum and pes planus Dislocation of the lens and a variety of congenital anomalies involving the heart and aorta are also frequently associated

(Courtesy of Dr G M MacKee)



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(Ormsby and Montgomery Diseases of the Skin Lea and Febiger)



Fig 92 POIKILODERMA VASCULARE ATROPHICANS

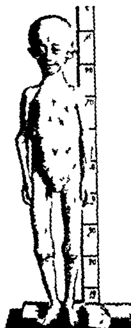
Although this condition is usually consistent with good general health patients who have it tend to develop either mycosis fungoides or another lymphoblastomatous process with increased frequency The dry and atrophic x ray skin also shows pigmentation telangiectases and photosensitivity It may also undergo ulceration

Fig 93 GARGOYLISM (HUNTER HURLER DISEASE)

This two year nine month gargoyle has a height age of twenty-one months He shows the coarse features large asymmetric skull corneal *clouding and myxedematous type of skin that* are also associated with the disorder Other typical features found in this patient included hepatosplenomegaly *flexion of the joints* and chondrodystrophic changes



(Williams Textbook of Endocrinology)



(Atkins New England Journal *of Medicine vol 50 1954*)

Fig 94 PROGERIA

The classic features of progeria are apparent in this eight year five month old patient These include dwarfism loss of hair prominent scalp veins exophthalmos a small face a beaklike nose *diminished subcutaneous fat* muscular atrophy arthritic joint changes and the general impression of premature senility He died three years later of an acute *myocardial infarction due to severe coronary artery disease* (a complication to which these individuals are highly prone)

(Ormsby and Montgomery Diseases of the Skin Lea and Febiger)



Fig 92 POIKILODERMA VASCULARE ATROPHICANS

Although this condition is usually consistent with good general health patients who have it tend to develop either mycosis fungoides or another lymphoblastomatous process with increased frequency The dry and atrophic x ray skin also shows pigmentation telangiectases and photosensitivity It may also undergo ulceration

(Wintrobe Clinical Hematology Lea and Febiger)

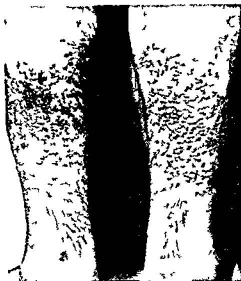


Fig 97 GAUCHER S DISEASE

The patient with Gaucher s disease here photographed shows the pingueculae that could give the clinician a clue as to the presence of this lipoidosis In fact this finding may be decisive in the infantile form (in which there is no pigmentation) when the possibility of Niemann Pick s disease is raised Although xanthomas do not occur in Gaucher s disease there may be other dermadromes in the form of bronzing of the skin purpura chloasma like spots and leg ulcers

Fig 98 LOCALIZED AMYLOIDOSIS

This dermatosis is illustrated in its typical form to point out its benignity (in contrast to the generalized type of amyloido is) and its re emblance to neurodermatitis and lichen planus The hard transparent and markedly pruritic nodules and papules tend to form infiltrated plaques especially on the legs Note the dark staining in the area biopsied resulting from the local injection of Congo red



(Courte y of Dr Ruben Noml nd)



(Major and Delp Physical Diagnosis)

Fig 95 THE MIKULICZ SYNDROME

Such enlargement of the parotid glands might represent the symptomatic involvement by a lymphoma (as is the case in the patient here shown) leukemia tuberculosis sarcoidosis systemic lupus erythematosus or amyloidosis It may occur as a primary disorder of the salivary glands (the Mikulicz disease) in which situation it is often associated with the sicca syndrome and a chronic polyarthritis Asymptomatic noninflammatory parotid enlargement can also be observed in association with malnutrition and protein depletion obesity liver disease and impaired glucose tolerance

Fig 96 LIVEDO RETICULARIS ASSOCIATED WITH ACUTE PANCREATITIS

This photograph was taken on the eleventh day of a recurrent bout of pancreatitis proved both chemically and by autopsy In addition to the reticulated brownish gray abdominal and chest discoloration illustrated (known as Walzel s sign) acute hemorrhagic pancreatitis may become manifest on the skin in the form of localized areas of bluish discoloration about the umbilicus and in the loin (the Gray Turner sign)



(Sigmund and Shelley New England Journal of Medicine vol 251 1954)

(*Continuation of text from page 514—preceding "Atlas"*)

Hemochromatosis is characterized by bronzing of the exposed skin, in part due to the extensive hemosiderin depositions (Figure 52) Much of the pigmentation in hemochromatosis is actually melanin, however, and not iron as one might expect It may be associated with diabetes mellitus or other endocrinopathies (pp 60 and 540) Since the mucous membranes can be discolored in hemochromatosis, this site of involvement cannot serve to differentiate it from Addison s disease

Many types of *intracranial disease* are known to produce *generalized cutaneous pigmentation* The list includes Schilder's disease, schizophrenia, encephalitis ependymoma of the third ventricle, hepatolenticular degeneration, and pituitary tumors (in the presence of normal adrenals) It is postulated that the melanin stimulating hormone produced by the pars intermedia of the pituitary is the common pathway for this response via the hypothalamohypophyseal tract [139, 1405] It must be recognized that some of the antiepileptic drugs, most notably Mesantoin, are capable of producing a diffuse brownish pigmentation, this effect usually subsides after cessation of the medication [1404]

A variety of skin discolorations also offer clues to *other neurologic diagnoses* An underlying neuropathy may be deduced from the *postherpetic pigmentation* along the distribution of the intercostal or trigeminal nerves Loss of hair pigment and alopecia areata are also seen in the latter instance Large café au lait (milk coffee) spots tend to be a prodromal sign, preceding the tumor formation in *neurofibromatosis* (von Recklinghausen s disease) (pp 383 and 543) [1146] In addition to the café au lait spots ('the hallmark of neurofibromatosis"), there may be a prominent tendency to freckling and a diffuse pigmentation of the skin (graying or bronzing) A hairy pigmented area over the lower spine suggests a *spina bifida occulta* White and cold changes in the fingers, toes, nose, and tips of the ears may presage *Raynaud's disease* (p 219) Intensification of this discoloration to a bluish gray cyanosis and eventually a blackening of the skin denotes the impending development of gangrene (Figure 40)

Certain *drugs and chemicals* may cause discoloration or staining of the skin At times this reaction will disappear soon after cessation of the therapy or the exposure Most of these changes have little significance, however, except when the heavy metals also induce systemic disturbances (See Group II, pp 64 to 69 and 537) Several of these metallic pigmentations will be briefly cited

Slate gray areas of the skin and the blue-line on the gingival margins (resembling the lead line) sometimes follow *bismuth therapy* A dirty slate gray discoloration especially about the eyelids and facial folds may be associated with the introduction of the *mercurial compounds* The hyperpigmentation of *arsenical toxicity* (Figure 37) probably results from the mobilization of melanin to some areas while depigmentation occurs in others The *coal tar derivatives* may induce morbilliform or papular eruptions which are occasionally followed by pigmentation at these sites Reference is also made to the diffuse brownish pigmentation, particularly of the face due to *Mesantoin therapy* [1404]

(Soffer Diseases of the Endocrine Glands Lea and Febiger)



Fig 99 LUTEINIZATION OF THE OVARIES

This thirty-one year old woman showing marked facial hirsutism and obesity was found to have diffuse luteinization of the ovaries Derangement of either adrenal or ovarian function can result in true endocrinopathic virilism It is again stressed that hirsutism in itself is not necessarily diagnostic of an endocrinopathy especially when dealing with certain races a familial history of hirsutism and the persistence of normal menstrual periods

THE ERYTHEMAS AND PURPURAS

Erythematous dermadromes are closely related to systemic diseases but more often the association is tenuous and the cause obscure A scarlatiniform erythema consisting of large bright red areas which occasionally become exfoliative is sometimes associated with gastrointestinal and toxic conditions Erythema gyratum perstans will be discussed with the neoplastic dermadromes (p 541)

Erythema and the eczematous dermatitides are frequently associated with *allergic phenomena* The urticaria and generalized scarlatiniform or morbilliform eruptions due to penicillin sensitivity are classic Many of these drug eruptions and reactions have been previously discussed in Group II (p 62)

Erythema multiforme consists of macular papular, bullous or urticarial lesions of various sizes and shapes, which in some cases appear as purplish red plaques (Figures 8 and 9) Iris type lesions on the forearms and extensor surfaces are characteristic There is a seasonal, recurrent form of simple" erythema multiforme, but this form is rather unusual in early childhood

This dermadrome may also be associated with gastrointestinal diseases, drug toxicity (including the digitalis preparations)[403b] infections and radiation therapy for cancer The persistence of erythema multiforme like lesions on the skin and mucous membranes, including the migrating type, should raise the possibility of the parasitic eosinophilic granulomas and the Loffler syndrome (p 64) Other causes of symptomatic erythema multiforme include the drug eruptions rheumatic fever brucellosis serum sickness, endocarditis, infectious mononucleosis, and ulcerative colitis

Erythema multiforme exudativum also affects the urethra the conjunctivae, the joints and the mucous membranes It has many clinical variations and descriptive designations Of these disorders, the Stevens Johnson syndrome (Figure 4) and Reiter s disease are best known (See Group V, p 161)

Erythema nodosum or dermatitis contusiformis (Figure 5) consists of erythematous hard symmetrical subcutaneous nodules over the extensor surfaces of the arms buttocks and shins In contrast to erythema induratum this lesion does *not* break down and ulcerate Erythema nodosum is a nonspecific reaction that has been associated with drug reactions (iodides, bromides sulfonamides) ulcerative colitis[170] and with various infections including streptococcosis tuberculosis, and those of spirochetal fungal and viral origin (See Group X, p 313)

Urticaria or hives is a common manifestation of allergy, presumably due to the local release of histamine or histamine-like substances which result in increased capillary dilatation and permeability The lesions are usually pruritic and transient, consisting of large or small erythematous and edematous macules or wheals Dermographism and angioneurotic edema are also urticarial phenomena The former appears at friction sites in sharply defined linear patterns, the latter as circumscribed subcutaneous swellings (usually about the face) that may persist for a week or more

The vast array of conditions that give rise to urticaria can be deduced

Argyria

Argyria resulting from the chronic therapeutic use of silver salts for either gastric or nasal symptoms is emphasized at this point The steel blue or gray color imparted to the exposed areas of the skin has not infrequently alarmed the unsuspecting physician at first glance Argyria can be readily distinguished from true cyanosis, however, by the following characteristics it is not a purple-blue, it is more intense around the mouth and the eyes, frank heart or lung disease is usually absent, and there is improvement of the patient's color with exercise (in contrast to an increase in the cyanosis when true cardiopulmonary disease is present) It should be stressed that *any* of the silver compounds given by *any* route may be the offender provided the exposure is sufficiently prolonged Argyria has at times also resembled the pigmentation of Addison's disease ochronosis, hemochromatosis, malignant melanoma, bismuthia, chrysiasis, and arsenical melanosis [15]

The generalized grayish or violaceous pigmentation resulting from *gold compounds* administered parenterally may very closely simulate that of argyria While it tends to affect the lower eyelids initially, it can develop on any part that is exposed to ultraviolet radiation

Carotenemia

Carotenemia is usually a benign disorder associated with the ingestion of excessive quantities of fruits and yellow vegetables (oranges carrots, spinach, kale, eggs and papaya) This pigmentation is prone to become accentuated in panhypopituitarism hepatic disease, diabetes mellitus, hypercholesterolemic xanthomatosis and myxedema either because of the poor utilization or oxidation of vitamin A precursors, or the existing disturbance in lipid metabolism It is characterized by a generalized yellowish tint, *especially apparent on the palmar and plantar calluses In females,* this discoloration is often first observed on the abdominal walls and over the buttocks In contrast to jaundice however, there is no scleral involvement Clinicians are most prone to encounter this disorder in times of meat shortage (as was the case in England during World War II), or when the above mentioned foods are consumed as part of reducing diets or in an attempt to improve vision Once the individual resumes a normal diet, the xanthodermia usually fades in two to six weeks

Sulfhemoglobinemia and Methemoglobinemia

Sulfhemoglobinemia and methemoglobinemia were also listed in Group XIII (p 384) These entities occasionally cause great confusion in a patient with severe cyanosis whose illness was initially thought to be cardiac or pulmonary in nature [1390, 1391] Both types of abnormal hemoglobin may be caused by the sulfonamides, phenacetin acetanilid, *sulfones pamaquin* pyridium, nitrites, sulfides sulfates and potassium chlorate The methods for their detection are described in Part II (p 694)

"butterfly" appearance of skin lesions that affect the cheeks and the nasal bridge area Such symmetry is less common in the localized discoid form of lupus erythematosus than in the disseminated form On many occasions, however, there may be little or no characteristic eruption in the disseminated form of the disease, a fact that has emerged with striking clarity from the impetus of the L E cell test It is also pointed out that a number of other dermatoses can manifest themselves in the "butterfly" pattern These include seborrheic dermatitis, rosacea, and polymorphous light sensitivity At times features of the first two disorders may be simultaneously present with lupus erythematosus but they never give rise to atrophy in themselves

Difficulty might be encountered in distinguishing between the cutaneous morphea of the subacute disseminated form of lupus erythematosus and discoid lupus which is attended by many extensive lesions The eruptions in the former instance tend to be more widespread and symmetrical, less sharply marginated, accompanied by a more intense erythematous edema and pigmentation, and associated with purpura Furthermore, the tendency to involvement of the elbows, knees, palms, and other pressure areas is at times quite pronounced in disseminated lupus When doubt exists a small biopsy taken from an active section of the plaque could be of assistance in making the differentiation In this regard, reference is made to the absence of collagen involvement and the finding of liquefaction degeneration in the region of the epidermal dermal junction—features which are fairly characteristic of discoid lupus The atypical morphology of psoriasis sarcoidosis lupus vulgaris, and secondary or tertiary syphilis may be confused with lupus erythematosus, but are correctly identified by biopsy and other ancillary findings

Purpura (Figure 6) (i e , an extravasation of blood into the subcutaneous tissues) can also be considered as an erythema The smaller lesions are pinpoint sized petechiae, while the larger ones may present as extensive ecchymoses Erythrodermas often accompany the purpuric expressions of systemic disease Purpuras resulting from coagulation defects are often superimposed upon a concomitant vascular injury The former may be related to a prothrombin deficiency a fibrinogen deficiency, the use of the anticoagulants or hemophilia and the ever increasing number of hemophilia like disorders (p 224) [818b, c]

Mills has reviewed 187 cases of childhood purpura seen at the Mayo Clinic [818a] These included 105 instances of thrombocytopenic purpura (of which 24 were secondary to infection, and 78 were of the idiopathic variety) and 82 instances of nonthrombocytopenic purpura (of which over one-half were of the anaphylactoid or allergic type)

The *nonthrombocytopenic purpuras* can be variously caused by drug reactions infections nutritional disturbances allergies amyloidosis [204] and a number of other entities (pp 224 and 225) A secondary nonthrombocytopenic purpura may be of grave consequence when associated with certain infectious diseases or drug toxicity Reference is made to the hyperglobulinemic purpuras, which include macroglobulinemia (p 187) and purpura hyperglobulinemica (p 187) One should also bear in mind several conditions that produce purpura as a result of the decreased blood vessel sup-

from its association with drug toxicity, various infections and fevers, parasitic infestations, endocrine disorders, gastrointestinal diseases, emotional upsets, necrotic neoplasms, and the lymphomatous diseases The urticaria of a drug reaction tends to be violaceous, with a serpiginous border and a predilection for the trunk When associated with infection or malignancy, the lesions are apt to be chronic, tender, and burning Urticaria evoked by psychogenic episodes usually develops in the afternoon and fades by morning

Urticaria pigmentosa is a chronic cutaneous disorder that may occur at all ages and is usually benign Clinically, it is characterized by pigmented macules, papules and on rare occasions by nodules Swelling and itching can accompany the rubbing of the lesions (Darier's sign) Microscopically, there is an increased number of cutaneous mast cells, but the pigmentation is noted to represent only an exaggeration of the usual melanin pigment It is felt that the urtication following stimulation of the skin represents the release of histamine from these underlying mast cells As a rule, urticaria pigmentosa is a relatively innocuous disorder in childhood, with the lesions tending to disappear in adult life

The systemic implications of this disease are being appreciated with increasing frequency in the American literature, particularly with reference to the osseous involvement (even suggesting metastatic cancer)[1389] Liver disease splenomegaly, diarrhea cachexia and bone marrow granulomas (due to the increased number of immature and postmature mast cells) have also been encountered Urticaria pigmentosa may require differentiation from leukemia cutis, the xanthomata, Letterer Siwe's disease, and various bullous eruptions

Although scaling is the prominent feature *psoriasis* may be regarded as an erythema An etiologic association between constitutional diseases and psoriasis has not been definitely established, notwithstanding the frequency of its coexistence with a unique form of arthritis

Of the other erythrodermas with exfoliative characteristics, mention is made of pityriasis rubra in which the erythema is followed by a branlike scaling over thickened or atrophic skin Pruritus may be pronounced These lesions are often identified with diseases of the leukemia-lymphoma group (Figure 25) and internal malignancy[650] When combined with xeroderma and follicular keratosis, they can also be indicative of a vitamin deficiency syndrome

Attention is repeatedly directed to *lupus erythematosus* in this book The localized, well defined, usually persistent, and often symmetrical erythema of the nose and cheeks ("butterfly" pattern) and the exposed portions of the arms and chest is apt to be a reflection of serious systemic involvement in a large proportion of these patients (Figure 68) The lesions are usually erythema multiforme-like, but they may also be pruritic, telangiectatic, or vesicular (*vide infra*) Involvement of the endocardium (Libman-Sacks syndrome) and the other viscera is reflected in symptoms suggestive of heart disease nephritis, rheumatoid arthritis, thrombocytopenic purpura and other serious constitutional disorders (See Group X, pp 304 and 545)[929, 930]

There are several pertinent observations concerning the so-called

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port by the extracapillary tissues These include senile purpura, cutis hyperelastica, and Kaposi's idiopathic hemorrhagic sarcoma—each of which will be subsequently discussed in this chapter

Also to be considered in instances of unexplained purpura is the damage to the vessel walls or the platelets or both because of some underlying immunohematologic derangement Aside from idiopathic thrombocytopenic purpura, these encompass severe infections (scarlet fever *Pseudomonas* infections, and the Waterhouse Friderichsen syndrome), drug purpura (especially to quinine, quinidine, the sulfonamides, iodides, and thiouracil), disseminated lupus erythematosus, the Henoch Schonlein syndrome, erythema multiforme, and polyarteritis Clinicians who maintain patients on quinidine should be aware of the immunothrombocytopenic purpura that can be induced by this particular drug [870] This complication is otherwise indistinguishable from the idiopathic form of thrombocytopenic purpura

Thrombocytopenic purpura is usually a manifestation of some serious underlying hematologic or systemic dyscrasia and requires prompt investigation (p 180) Extensive gangrene of the skin and subcutaneous tissues or the occurrence of a purpuric and ulcerating lesion adjoining an urticarial wheal in a patient with purpura suggests the possibility of *thrombotic thrombocytopenic purpura* (p 218) [98b]

It is important for clinicians outside of dermatologic circles to recognize promptly *the benign dermatologic purpuras* (p 225) This group of disorders usually affects the lower extremities in the form of punctate, pigmented macules papules and telangiectases The lesions are initially reddish, but then change to the brownish color of hemosiderin before fading Prolonged periods of involution and relapses may occur The fundamental defect is one of an increased capillary fragility Fortunately, the latter is infrequently associated with any overt hematologic abnormalities This group includes purpura annularis telangiectodes (Majocchi) progressive pigmentary dermatosis (Schamberg) pigmented purpuric lichenoid dermatosis (Gougerot and Blum), and angioma serpiginosum (Hutchinson) In 92 cases studied at the Mayo Clinic no constant and clear cut histologic differences could be found to warrant any further separation [820]

Senile purpura is encountered in elderly people with very thin skins It appears as dusky red lesions with sharp borders that are confined to the dorsum of the hands and forearms It is due to the loss of connective tissue support of the blood vessels This entity should not be attributed to cardiovascular disorders, deficiencies in the clotting mechanism or to vitamin C deficiency—as is almost always the case when physicians are not aware of this disorder

PRURITUS

Itching is a conspicuous dermal clue to many systemic diseases It is quite probable that endogenous circulating allergens, metabolites, or histamine-like toxic substances which are elaborated and released by tumors and inflammation retained secretions (bile), or impaired excretions (renal waste products) provide the low frequency stimuli in the cutaneous nerve endings

that initiate the process This can set up an itch scratch cycle that intensifies the nonspecific dermadrome The latter in turn, may progress to a prurigo-like lesion or a secondarily infected pyoderma As a result of this constant irritation, areas of hyperpigmentation and melanoderma sometimes develop with eventual neurodermatitis, lichenification, eczematization and alopecia

There is much evidence to support the contention that two types of itch and pain exist, namely (1) a superficial localized, and pricking sensation which corresponds to the "fast" pain of short duration after the application of the stimulus and (2) a diffuse, poorly localized and burning itch, corresponding to 'slow' pain (Pruritus is abolished by high frequency pain because the impulses immediately create the sensation of pain by their prompt relay to the same lateral spinothalamic tract Also, their spread to the neurons of the internuncial circuits tends to render the latter refractory) Recent studies of the itch mechanism by Shelley and others imply that certain chemical reactions in the skin resulting from proteolytic reactions may be of paramount importance in the mediation of pruritus There are two types of bound proteinases demonstrable in the skin These consist of the intracellular cathepsins within the epidermis which may be released by stimuli applied to this tissue and the circulating plasmin of the plasma which is released as a result of allergic and inflammatory reactions

The pruritus will usually subside when the primary cause is removed The predisposing causes of "physiologic pruritus" include such endocrine imbalances as hypothyroidism hyperthyroidism and those associated with menstruation, pregnancy, and the menopause Itching on a toxic metabolic basis is found in biliary and liver disease severe renal disease diabetes mellitus fevers, drug reactions malignancy and the leukemia lymphoma group of diseases Pruritus may be a possible clue to various neurogenic and psychogenic disorders, B avitaminosis arteriosclerosis polycythemia vera, certain anemias intestinal parasites gout and even tuberculosis It is stressed that the diagnosis of "senile pruritus' should be made with the greatest reserve in the presence of a severe and unexplained pruritus

Unexplained *prurigo like papules* scattered over the trunk and extremities with itching and pigmentation should raise the possibilities of Hodgkin s disease and lymphatic leukemia (Figure 26B) (pp 181 and 539) Successive crops with intensification of the itching have been observed These lesions should not be confused with such dermatitides as the papulonecrotic tuberculid or the scabetic pruritic and excoriated papulosis of pregnancy (prurigo gestationis)

The Xanthomatous Lesions

Xanthomata the classic dermadromes of the lipoidoses, are waxy, yellow, and nodular lesions composed of foam cells' They are usually associated with metabolic or endocrinal dysfunctions or both and consist of precipitated lipids or cholesterol [76-85] The color (which is also partly due to carotene) tends to disappear in the older lesions The hyperlipemia incidental to myxedema chronic pancreatitis the nephrotic syndrome and

serious liver damage (including cirrhosis and biliary obstruction) favors the formation of xanthomata

The discoloration in a number of unrelated entities may simulate the color of xanthic lesions The former include pseudoxanthoma elasticum traumatic fat necrosis, melanotic tumors, and hemorrhage within a lipoma, myxoma, or fibromyxoma Essential hypercholesterolemia, essential hyper lipemia, and lipoid proteinosis were discussed at some length in Group II (*pp 76 to 79*), and will be further considered in the second section of this chapter (pp 533 to 534)

The presence of hereditary hypercholesterolemia is suggested by *xanthoma tuberosum multiplex* (Figure 10) As the name implies, these are raised and irregular, papulated, hard, and sometimes pedunculated forms of the tumors They may occur at any age They have a predilection for the extensor surfaces of the elbows and knees, the tendon sheaths, the soles and the palms Other descriptive terms have been used to describe the different clinical forms of these lesions, including xanthoma planum, xanthoma papulosum, and xanthoma tumoriforme Severe atherosclerosis with vascular accidents is likely to occur

Xanthelasma is a yellowish, flat or slightly raised, soft xanthomatous lesion of the eyelids It is frequently a valuable clue to an associated disorder of fat metabolism or atherosclerosis

The papular eruptive xanthomata (xanthoma disseminatum) associated with either *idiopathic hyperlipemia* (of the Burger Grutz type) or *secondary hyperlipemia* need not be associated with xanthelasma, xanthoma tuberosum, or the involvement of tendons

Xanthoma diabeticorum (Figure 11) is an eruption of purplish red papules with yellow centers It appears during the course of uncontrolled diabetes mellitus and has a predilection for the extensor aspects, the palms, and the soles The lesions tend to fluctuate with the serum lipid levels and the control of the underlying diabetes [1399]

A dermadrome that can long antedate the onset of the other signs of diabetes is *necrobiosis lipoidica diabeticorum* (Figure 12) In this condition, there appears a red to brown, sharply outlined plaque with yellowish atrophic centers and a violaceous halo The lesions are usually located on the shins but occasionally occur on the upper extremities and trunk Although lipids may be deposited and xanthomas formed, hyperlipemia is not always present

Herpes and Herpetiform Lesions

Herpetic lesions consisting of closely grouped small and painful superficial vesicles, are usually associated with a lowered resistance of the local tissue Although the cause in some instances is obscure, filterable viruses seem to be responsible for most of the herpetiform eruptions

Herpes simplex (Figure 19) is a very common vesicular eruption usually circumoral in location A yellowish crust forms, and healing without scarring takes place in a few days Antecedent emotional upsets, fevers and gastrointestinal disorders are frequent The profound cutaneous, neurologic, and systemic manifestations of infection with this virus, including

eczema herpeticum (Kaposi's varicelliform eruption), have been discussed in both Group V and in the second section of this chapter (pp 160 and 550) The finding of the typical giant cells in tissue removed from the base of the vesicles distinguishes the latter entity from the morphologically similar eruption due to *generalized vaccinia* (p 789)[579]

Herpes zoster (Figure 18) begins as a very painful, and usually unilateral group of papules or vesicles on an erythematous base It assumes a somewhat linear arrangement along the course of one or several cutaneous sensory nerves in association with the posterior spinal ganglionitis Hemorrhage, ulceration and gangrene may complicate the lesion Although herpes zoster is commonly an independent disease, it is also frequently found to coexist with such systemic disorders as leukemia, Hodgkin's disease, the other lymphoblastomata, internal malignancy, and drug reactions (most notably arsenic)[516 651 1017]

Herpes zoster of the geniculate ganglion produces the *Ramsay Hunt syndrome* (p 542) This condition is characterized by severe facial palsy, involvement of the eighth nerve, and a vesicular eruption in the external auditory canal and on the faucial pillars The virus of herpes zoster has also produced a hepatitis[339b] Recent immunologic studies have confirmed the relationship or identity of this virus and that of varicella

Herpes gestationis is an itching burning herpetiform eruption that spreads radially from the lower abdominal wall It may be of serious consequence to the fetus during pregnancy, particularly during the last trimester Similar lesions have been noted in the presence of pathologic abdominal masses

A chronic form, known as *dermatitis herpetiformis* or *Duhring s disease* has a predilection for the trunk forearms, sacral region buttocks, and posterior axillary folds (Figure 20) It can run a course over months that is punctuated with exacerbations and remissions It is usually an intensely pruritic and burning lesion in which crops of blisters pustules, or erythematous patches may predominate There is often a residual pigmentation or scarring after healing A gonadal influence has been inferred from its tendency to affect males more commonly than females, and in view of its frequent occurrence in association with puberty, menstruation, pregnancy, and the menopause Halogen sensitivity appears to be the etiologic factor in some of these patients who have received medications containing bromide or iodide Psychogenic factors might also play a part Cirrhosis of the liver drug poisonings neoplasms, and radiation therapy are on occasion also associated with herpetiform eruptions[1394]

The Photodermatoses

Under certain conditions in which various metabolites function as photosensitizing substances exposure of the skin to sunlight or to ultra violet and other wavelengths can induce photodermatoses These cutaneous manifestations may serve as valuable clues in the diagnosis of the underlying systemic diseases This subject was recently well reviewed by Kesten and Slatkin[1393]

A classic example of such pigmentation is the dermatosis associated

serious liver damage (including cirrhosis and biliary obstruction) favors the formation of xanthomata

The discoloration in a number of unrelated entities may simulate the color of xanthic lesions The former include pseudoxanthoma elasticum, traumatic fat necrosis, melanotic tumors, and hemorrhage within a lipoma, myxoma, or fibromyxoma Essential hypercholesterolemia, essential hyperlipemia, and lipoid proteinosis were discussed at some length in Group II (pp 76 to 79), and will be further considered in the second section of this chapter (pp 533 to 534)

The presence of hereditary hypercholesterolemia is suggested by *xanthoma tuberosum multiplex* (Figure 10) As the name implies, these are raised and irregular, papulated, hard, and sometimes pedunculated forms of the tumors They may occur at any age They have a predilection for the extensor surfaces of the elbows and knees, the tendon sheaths, the soles, and the palms Other descriptive terms have been used to describe the different clinical forms of these lesions, including xanthoma planum, xanthoma papulosum, and xanthoma tuberiforme Severe atherosclerosis with vascular accidents is likely to occur

Xanthelasma is a yellowish, flat or slightly raised, soft xanthomatous lesion of the eyelids It is frequently a valuable clue to an associated disorder of fat metabolism or atherosclerosis

The papular eruptive xanthomata (xanthoma disseminatum) associated with either *idiopathic hyperlipemia* (of the Burger Grutz type) or *secondary hyperlipemia* need not be associated with xanthelasma, xanthoma tuberosum, or the involvement of tendons

Xanthoma diabeticorum (Figure 11) is an eruption of purplish red papules with yellow centers It appears during the course of uncontrolled diabetes mellitus and has a predilection for the extensor aspects, the palms and the soles The lesions tend to fluctuate with the serum lipid levels and the control of the underlying diabetes [1399]

A dermadrome that can long antedate the onset of the other signs of diabetes is *necrobiosis lipoidica diabeticorum* (Figure 12) In this condition, there appears a red to brown, sharply outlined plaque with yellowish atrophic centers and a violaceous halo The lesions are usually located on the shins but occasionally occur on the upper extremities and trunk Although lipids may be deposited and xanthomas formed, hyperlipemia is not always present

HERPES AND HERPETIFORM LESIONS

Herpetic lesions, consisting of closely grouped, small and painful superficial vesicles, are usually associated with a lowered resistance of the local tissue Although the cause in some instances is obscure, filterable viruses seem to be responsible for most of the herpetiform eruptions

Herpes simplex (Figure 19) is a very common vesicular eruption usually circumoral in location A yellowish crust forms, and healing without scarring takes place in a few days Antecedent emotional upsets, fevers and gastrointestinal disorders are frequent The profound cutaneous neurologic, and systemic manifestations of infection with this virus, including

posure to potential occupational carcinogens (arsenic tar, x ray, etc) offer an important field for preventative medicine These lesions include alopecia atrophy, eczema keratoses, verrucae, ulcerations leukoderma, melanoderma and sclerodermatous changes [1170d]

Leukoplakia of the mouth should not be confused with lichen planus Biopsy should always be carried out under such circumstances, particularly when erosion or fissuring complicates patches of leukoplakia Hyperkeratoses of the palms and soles are often indicative of *chronic arsenical poisoning* (Figure 37) These lesions are subject to malignant degeneration External exposure to arsenic can also occur from the use of tree sprays where no precautions are used

It is usually very easy, but quite important, to differentiate benign *seborrheic keratoses* ("senile warts) from both senile keratoses and nevi (since seborrheic keratoses are prone to blacken with age) A little friable matter can usually be readily scratched off, in contrast with the densely adherent keratin layer of senile keratoses

The incidence of *melanocarcinoma* tends to be much higher in certain skin types, viz those who readily develop sunburns and freckles and persons with delicate blonde or sandy skins Females are also more susceptible Furthermore these individuals are prone to experience a much more fulminant type of this malignancy Reference was previously made to the unique cutaneous pigmentation of malignant melanoma (p 513), and of the great diagnostic elusiveness of this neoplasm (p 328) The feet and legs are common sites for the development of a melanoma Difficulty is often encountered in locating the primary lesion on the skin when it arises in certain sites (most notably the scalp and the anus) On several occasions the author has encountered instances of a pyogenic granuloma that was mistaken for a melanoma

The small white or yellow cutaneous nodules of the highly autoinoculable virus infection causing *molluscum contagiosum* are usually very characteristic Nevertheless, they have been confused with furuncles and various tumors

Of some importance are the *fibromas*, consisting of tumors and nodules of various size, shape and consistency and composed of hypertrophic connective tissue *Neurofibromatosis* should be considered if the fibromas are multiple, soft and flesh colored to brown (Figure 28)

Subcutaneous nodules near the joints and tendons, especially the elbows and knees may be important clues to *rheumatoid arthritis rheumatic fever*, or *scleroderma* In rheumatic fever the nodules (Figure 21) are dusky red, movable nontender and tend to appear on the hands, face scalp and ears *Tophi* (Figure 51) are hard subcutaneous nodules of the external ear finger joints, and other areas they are practically pathognomonic of gout

Specific nodules and tumors (Figures 24, 25 and 26) frequently occur in the lymphoma leukemia group of diseases [651] The cutaneous infiltrates or nodules of certain leukemias are often specific—even for long periods before the characteristic blood changes can be found The tumor stage of *mycosis fungoides* is usually preceded by a "premycotic or prefungoid ' phase in

with *pellagra* (Figure 46) It begins as a dull red erythema limited to the exposed surfaces which eventually becomes scaly and pigmented a deep gray-brown hue Lesions on the exposed skin in *lupus erythematosus* and *drug sensitivities*—particularly in the case of the sulfonamides, the coal tar dyes, the barbiturates, gold, chlorpromazine, and quinine[1164b]—are also secondarily influenced by sunlight Other systemic conditions that have been associated with photosensitization include infection with herpes simplex, hyperthyroidism, menstrual disturbances, scleroderma, and dermatomyositis

The incidence of *polymorphous photosensitivity* appears to be increasing While the eruptions may be similar, the rapid defervescence of this disorder once the exposure to sunlight or to artificial ultraviolet light is terminated differs from the little response that is forthcoming in the case of lupus erythematosus

Xeroderma pigmentosum is probably a hereditary anomaly that renders the exposed areas of the skin sensitive to certain invisible wavelengths Initially, the skin becomes dry, scaly, and rough, then dark to black freckling takes place Eventually, a radiodermatitis-like lesion appears, consisting of whitened atrophic areas with enlarged capillaries and verrucous excrescenses that are predisposed to malignant change (namely, basal cell epitheliomas, squamous cell epitheliomas, sarcomas, and even endotheliomas)

Negroes are not necessarily immune to xeroderma pigmentosum Inasmuch as a single recessive gene appears to transmit this disorder, one must regard extensive freckling among the apparently normal siblings with much interest as potential "formes frustes" Other extracutaneous abnormalities are encountered in this disease These consist of epilepsy, mental deficiency, deafness, and malformations of the joints

Extreme light sensitivity of the skin with a vesicular erythema, blistering, pronounced tanning, and epidermolysis bullosa like lesions are suggestive of *porphyria* (Figure 17) [17 2 2] The photosensitizing agent in this instance is a breakdown product of hemoglobin A pink to brown discoloration of the teeth (Figure 16) anemia, polyneuritis, and gastrointestinal disturbances may occur in the more severe cases of porphyria Liver damage seems to be a requisite for the majority of these manifestations (and perhaps in many of the other light sensitizations of the skin as well) In *congenital porphyria* the commonest cause of hydroa vacciniforme, uroporphyrin type I is found in the urine and feces as well as increased amounts of coproporphyrin but porphobilinogen is absent (See Group II, pp 61 and 62) Boys are apparently more susceptible to hydroa aestivale (Figure 15) Considerable scarring and deformity may accompany the severe and recurrent cases, even leading to corneal scarring and blindness

Tumors and Nodules

The necessity for multiple biopsies is stressed when a large lesion is suspected of undergoing malignant changes This applies in particular to long standing burns and 'stasis' ulcers Similarly, the cutaneous stigmata of a host of precancerous lesions that are the result of the individual s ex

posure to potential occupational carcinogens (arsenic tar, x ray, etc) offer an important field for preventative medicine These lesions include alopecia, atrophy, eczema keratoses verrucae ulcerations leukoderma melanoderma, and sclerodermatous changes [1170d]

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which the lesions may simulate those of psoriasis, seborrheic dermatitis, eczema, erythema multiforme, pityriasis rubra, erysipelas, and leprosy

Malignant cutaneous or subcutaneous neoplasms (Figure 24) should initiate studies to locate a possible primary site The *sentinel or Virchow's node* in the supraclavicular region is a good example of a palpable metastatic lesion that may be the first clue to an occult primary cancer within the abdomen

Multiple idiopathic hemorrhagic sarcoma (Kaposi's sarcoma, Figure 23) is an angiosarcoma that commences as tender reddish, purplish, or bluish black macules on the forearms, hands, legs, and feet The lesions then slowly develop into nodules which have a rubbery consistency and often coalesce Bullae may be superficially mimicked Although these tumors are now regarded as neoplasms that arise multicentrically from the undifferentitated perithelial tissue of the vessels rather than as true malignant sarcomas, sarcomatous changes of various types may occur in one or several of the lesions In fact, while clinical remissions do occur, many of these patients will ultimately die of reticulum-cell sarcoma

The presence of this condition should suggest the possibility of other sarcomatous tumors in the gastrointestinal tract, the mesenteric lymph nodes, the liver, the lungs, the bones, and the central nervous system [1385] It is not yet widely appreciated that gratifying remissions can be produced both in this disease and in mycosis fungoides by high energy cathode rays In a review of 13 cases of Kaposi's sarcoma 6 patients had either frank diabetes or exhibited some evidence for this metabolic derangement [1400]

NAIL CHANGES

Astute clinicians and dermatologists have noted unique changes of the nails and their surrounding tissues in a number of systemic conditions Actually, abnormalities of the nails can be associated with practically every severe systemic disorder, whether it be anemia infection, a dietary deficiency, dysendocrinism, drug reactions excessive radiation, chronic poisoning, circulatory disorders, emotional disturbances, or the degenerative diseases

Many of these changes are not specific, as is the case with the longitudinal ridging and splitting (onychorrhexis) and the transverse furrows (Beau's lines) Nevertheless they may still be helpful, both diagnostically and in determining whether the patient's course is improving or deteriorating Contact irritants, local trauma, familial variants, and congenital anomalies must always be taken into consideration The reader would profit from a study of Ronchese's skeptical and objective evaluation of the "peculiar nail anomalies," primarily because of the caution advised against overinterpreting their significance [1395]

It is possible to date the onset of some systemic disorder that resulted in the appearance of Beau's lines by bearing in mind the following two facts (1) the nails tend to grow approximately *1 mm a week and (2)* about one month must transpire before the nail can be visualized beyond the proximal nail fold

Several fairly characteristic nail changes in conditions that are not basically "dermatologic diseases" are set forth in the following listing

1 *Spoon nails* or koilonychia can appear in hypochromic anemia, hypothyroidism, hyperthyroidism, acromegaly, polycythemia, secondary syphilis, nutritional deficiencies, and circulatory disorders, or they may be congenital The nail plates are thin, concave brittle, and loose Multiple laminations of the tips (onychoschizia) may also be noted

2 A slate-blue discoloration of the nail bed or matrix occurs in *argyria*

3 Transverse white bands, often referred to as Mee's lines, have been identified with *arsenic intoxication*[25] These changes are also observed in other conditions, such as Hodgkin's disease and high fevers[1395]

4 Since the nail matrix is highly radiosensitive, a variety of nail changes may be the first clinical evidence of *overexposure to both x rays and radioactive substances* These include onychorrhexis, discoloration, increased friability (hapalonychia), atrophy, and transverse ridging

5 Similar nail changes can occur in both *hypothyroidism* and *hyper thyroidism*—namely brittleness, loosening of the distal ends (onycholysis), longitudinal ridging, and koilonychia (Figure 31)

6 Nail atrophy and psoriasiform erosions of the nail plates occur in *hypoparathyroidism* (Figure 30)

7 Edwards has described the specific nail changes in both the *vasospastic and the organic peripheral vascular diseases* An extensive pterygium that obliterates the normally distinct boundaries between the nail fold and cuticle, and between the cuticle and nail plate, characteristically occurs in the vasospastic disorders (Raynaud s disease scleroderma)[1396] (It is well to bear in mind that a pterygium may normally be seen over the last two toe nails) Poor growth, thickening discoloration, and distortion ("claw nail") appear in the nails when organic arterial disease is present

8 *Clubbing of the fingertips* (Figure 34) is characterized by antero-posterior thickening, curving of the nail plate, and edema with increased connective tissue at the base of the nails[1397] This has been associated with endocarditis, chronic pulmonary infections, the cyanotic types of con genital heart disease, pyelonephritis, intoxications, cholangitis, regional ileitis, ulcerative colitis, and metaplasia of the urinary bladder mucosa (p 326)[1037 1039] Unilateral clubbing may be a valuable early clue to the presence of a superior sulcus tumor, an arteriovenous aneurysm, and a subclavian or innominate artery aneurysm Simple hypertrophy involving all the nails (onychauxis) occurs in acromegaly Care must be taken, however to avoid misdiagnosing or overemphasizing familial clubbing of the nails particularly in teen aged males

9 Paired white bands on the third and fourth fingernails which are neither palpable nor indented have been described in association with the *hypoalbuminemia* due to a variety of causes This sign could be particularly useful in differentiating the edema in these state (especially the nephrotic syndrome with a serum albumin of less than 2 2 gm per cent) from cardiac edema[1398]

10 The subungual "splinter hemorrhages in *subacute bacterial endocarditis* and *trichinosis* (Figure 32) are accepted as valuable clinical signs

They may occur in rheumatic heart disease, however, in the absence of valvular infection (p 115)

11 The nails are apt to be either absent or markedly deformed in the patient with a *congenital ectodermal defect* (p 419)

12 It is very important to recognize and biopsy a *subungual melanoma* (melanotic whitlow) as soon as possible, because of the more favorable opportunity for cure in this form of melanoma The early light brown discoloration in the nail fold, the eponychium, or the matrix can furrow or uplift the adjacent nail Local ulceration tends to occur late Unfortunately, this lesion is frequently treated for months as a fungus infection, during which time extensive metastases may have taken place

13 *Neuronychia* represents one of the few overtly demonstrable somatic manifestations of severe anxiety states and emotional disease In these disorders, superficial pitting, thinning, or splitting are often observed, along with separation of the nails from their bed

Miliaria and Anhidrosis

The author is continually impressed with the little attention devoted to the highly important subject of *miliaria* (the generic designation for all skin changes arising as a result of sweat retention) and the related entity of *tropical anhidrotic asthenia* as the basis of severe constitutional disorders The reader is referred to the writings of Shelley for fine reviews on the subjects of miliaria[1406] and anhidrosis [1407]

O Brien is of the opinion that there are two distinct types of anhidrosis related to heat [1408] *One stems from an intrinsic central failure of the sweating mechanism*, and is associated with heat hyperpyrexia The other is the peripheral obstructive type that is associated with miliaria and its sequelae, tropical (postmiliarial) anhidrosis and anhidrotic asthenia (p 106) Since it lowers heat tolerance by the ensuing fatigue or failure of the sweat mechanism miliaria also predisposes toward heat hyperpyrexia

As is the case with the designation "acne" there are several clinical types of miliaria depending on the site and degree of sweat retention and the secondary pathologic changes induced (viz, m crystallina m rubra, m pustulosa, and m profunda) In the primary types of this disorder, *abnormal keratinization and a resultant occlusion of the sweat duct orifices* is induced by the prolonged maceration and irritation of the skin from the sweat Miliaria tends to be a self perpetuating process, since the degenerated sweat-duct units mechanically occlude other units as they regenerate *The cardinal sign in all the miliarias is the increase in the size of the papules following vigorous sweating* This is most prominent in miliaria profunda, which is usually seen in patients suffering from tropical anhidrotic asthenia

The potential ramifications and clinical scope of this problem are enormous when considered in light of the following the stationing of many service personnel in subtropical and tropical areas, the predisposition of patients with extensive dermatoses to anhidrosis—particularly when the skin is further injured by excessive bathing the excessive use of soaps or detergents, the irritation of clothing, and the damage induced by irritating

topical medications, the occurrence of recurrent bouts of miliaria rubra in overheated homes during the winter months, and the numerous medical disorders that predispose to serious anhidrosis (*vide infra*) The excessive and prolonged use of shake lotions—especially those containing phenol, alcohol, or sulfur—can result in severe drying of the skin It is of interest that the native populations in the tropics are rarely affected by the sweat retention syndromes The acute and extensive bullous impetigo following a pustular miliaria has been referred to as ' monkey pox "

The following are some systemic disorders which can contribute to significant anhidrosis Addison s disease, cirrhosis, extreme dehydration, diabetes insipidus diabetes mellitus, glomerulonephritis heart failure, hypertension, orthostatic hypotension, myxedema malignancy, Simmonds' disease many poisonings, and the Sjogren syndrome A variety of disorders of the brain, the spinal cord or the peripheral nerves that interrupt the normal reflex pathways for sweating (e g , polyneuritis, leprosy anticholinergic drugs vascular and neoplastic diseases of the brain sympathectomy, syringomyelia multiple sclerosis cord transection) can also predispose to the development of anhidrosis [1407]

Hypertrichosis

The persistence of normal menstrual periods in women who are concerned about hypertrichosis [8] (Figure 99)—especially those of Latin or Jewish origin, and when a familial background exists—tends to confirm the presence of essential hirsutism It is furthermore emphasized that hirsutism *per se* is a much less secure manifestation of true endocrinopathic virilism than are other features (viz , changes in the voice enlargement of the clitoris decrease in the size of the breasts and the like) (Also see pp 28 35 and 532)

For the reasons cited in Group XIII in the discussion of radiation hazards x rays should not be employed as a means of producing permanent epilation On occasion hypertrichosis is encountered as a feature of other disorders *These include both forms of porphyria (i e the congenital* and the delayed cutaneous types) brain tumors, adenoma sebaceum multiple sclerosis, dermatomyositis, and encephalitis

The Tongue as an Indicator of Systemic Disease

While the tongue is not strictly a portion of the skin or its appendages the readiness with which it can be inspected justifies its consideration here The number of disorders that affect this highly vascularized muscular organ is legion Only those of general medical interest to clinicians will be cited The importance of recognizing and reassuring patients about the nature of the several minor congenital malformations to which the tongue is heir should be stressed *in order to avoid undue* concern by overanxious individuals For example the innocuous geographic tongue should not be confused with either leukoplakia or lichen planus affecting this organ Similarly the insignificant grooved (scrotal) tongue or a median rhomboid

glossitis should not be diagnosed as an atrophic glossitis or a neoplasm of the tongue

Furred Tongue There has undoubtedly been too much emphasis upon the significance of a furred tongue as an index of gastrointestinal and other disease Such factors as failure of normal mastication and salivation, a liquid diet, smoking, and fever can in themselves produce this change[1416] The 'strawberry" tongue in scarlet fever exhibits the engorged red fungiform papillae situated adjacent to the white thickened filiform papillae

Lingua Nigra There is a greater incidence of lingua nigra in recent years due to the increased use of antibiotic lozenges

Burning Tongue Perhaps the commonest cause of a burning tongue is the habit of rubbing the tongue against a calculus deposit or dentures It should be borne in mind that the complaint of a painful, burning tongue or some other tongue fixation is also a frequent feature in anxious postmenopausal women (who are often excessively preoccupied with a fear of malignancy) In fact, in one series of over 4700 cases of disorders affecting the skin and mouth described by McCarthy and McCarthy, a primary psychosomatic diagnosis was made in 11 per cent (the greatest number consisting of cancerophobia and a self induced papillitis involving the fungiform papillae at the dorsum of the tongue)

Chronic Acquired Macroglossia The causes of chronic acquired macroglossia include acromegaly, myxedema, the bald tongue of syphilitic glossitis, tuberculous glossitis, primary systemic amyloidosis, scleredema adultorum, pellagra, the other B avitaminoses, and lingual carcinoma There is much evidence for the precancerous nature of a luetic glossitis (Figure 33)

Atrophic Glossitis An atrophic glossitis stemming from the desquamation of the filiform papillae (and to a lesser extent of the fungiform papillae) characteristically occurs in the B avitaminoses, pernicious anemia, sprue, iron deficiency (the Plummer-Vinson syndrome), chronic dysentery, and intestinal strictures or fistulae

Neurologic Disorders Changes in the tongue may be an important sign in the diagnosis of certain neurologic disorders The latter include pseudobulbar palsy, bulbar palsy, lesions affecting either the hypoglossal nucleus or the hypoglossal nerve, alcoholism, senility, chorea, paralysis agitans, and evidence of tongue biting in epilepsy

Jaundice Pallor, Engorgement of the Veins and Cyanosis These are best observed on the under surface of the tongue Whereas purpuric lesions may occur in this area they rarely make their appearance on the dorsum

Air Embolism Blanching of half of the tongue (the Liebermeister syndrome) may be diagnostic of air embolism

Dryness of the Tongue Dryness of the tongue is not only evidence for true dehydration (if oral breathing and excessive talking are excluded), but also can be the result of disease affecting the salivary glands (mumps, Boeck's sarcoid, the Mikulicz Sjogren syndrome)

Lingual Thyroid Gland On rare occasions, a functioning lingual thyroid gland might be encountered

Telangiectases The characteristic telangiectases of familial telangiectasia (Figure 41) may be observed on the tongue

Mucocutaneous Dermatoses Mention is made of the following mucocutaneous dermatoses that can also involve the tongue lichen planus, erythema multiforme, pemphigus, and lupus erythematosus of both the discoid and disseminated types

SYSTEMIC DISEASES AND THEIR ASSOCIATED DERMADROMES

THE ENDOCRINOPATHIES

(Also see Group I)

The Pituitary

Pituitary dysfunctions may exhibit dermadromes similar to those resulting from primary disorders of thyroid, parathyroid, adrenal, or gonadal origin

Hyperpituitarism In acromegaly, the skin is pigmented, freckled coarse and furrowed This is especially notable as gyrate folds of the scalp In addition to the enlarged bones and soft tissues one may observe comedones coarse hypertrichosis (Figure 99) and spoon nails

Basophilic Adenoma The dermadromes are similar to those of hyperadrenalism (the Cushing syndrome) (Figures 58 and 59)

Hypopituitarism The skin is usually smooth, soft, and freckled in the exposed areas Alopecia of the vertex, lateral eyebrows, axillae, and pubes occurs, along with a dystrophy of the nails (Figure 57) In pituitary cachexia, the skin tends to be pale-yellow, and either smooth and thin, or coarse, dry, and crusted The hair frequently becomes sparse

The Thyroid

Hyperthyroidism The skin is likely to be smooth soft, warm, moist, flushed, sweaty, and severely pruritic Alopecia areata and urticaria with a persistent red dermographia over the thyroid gland itself (Maron's sign) are not unusual Either hyperpigmentation (especially of the eyelids) or vitiligo can be prominent in hyperthyroidism An elevated, circumscribed, nodular or tuberous, hard nonpitting edema (Figure 53) resembling pigskin or an orange peel may develop over the anterior tibiae, the color ranges from normal to brownish The occasional patient with hyperthyroidism demonstrates such sensitivity to sunlight that severe blistering has followed short exposures The brittleness and loosening of the distal ends of the nails may be striking (Figure 31)

Hypothyroidism The skin is generally cool, dry, waxy, and pruritic The hands tend to be rough, dry and cold, and the palms sallow Yellow xanthomatous lesions (Figures 10 and 11), isinglass-like pretibial scaling diffuse myxedema, eyebrow alopecia, sparse brittle hair carotenemia, prominent supraclavicular fat pads, and dystrophy of nails (Figure 31) are additional associations In cretinism, these dermadromes are greatly intensified Hirsutism is at times noted in juvenile hypothyroidism [31]

The Parathyroids

Hyperparathyroidism Calcinosis cutis with single or multiple hard nodules and plaques over pressure points, especially on the arms, may be found either in this disease or in hypoparathyroidism (Figure 50)(p 23) Ulceration with extrusion of calcium deposits can occur

Hypoparathyroidism A dry, scaly, and pigmented skin together with scanty hair and transverse grooving of the nails are the important cutaneous features in this condition (Figure 30) Moniliasis (Figure 81) also frequently accompanies the juvenile form of this disease[13]

The Adrenals

Hyperadrenalism Hyperadrenalism is suggested by the acne, the facial plethora, the abnormal distribution of fat (i e, a large panniculus), and the reddish to purple abdominal striae that are characteristic of the Cushing syndrome There is frequently deep pigmentation in the folds overlying the joints of the hands Females may demonstrate hypertrichosis (Figure 59) along with a 'buffalo hump and male type of hirsutism (One should remember that while hypertrichosis is associated with acromegaly, adrenal hyperfunction or tumors, and ovarian dysfunction or tumors, it more often represents a familial trait) Darkened areolae occur in the male Purpura, acrocyanosis, brownish pigmentation and poikiloderma like changes have also been observed

Hypoadrenalism Hypoadrenalism may be manifested by the addisonian hyperpigmentation (Figure 55) of the normally dark skin, the pressure or friction areas the palmar creases, the knuckles scars, and the mucous membranes (Figure 56) Coexisting vitiliginous spots or numerous black freckles and moles are sometimes present There may be pubic and axillary alopecia (Figure 57)

Pheochromocytoma Pheochromocytoma has been associated with multiple neurofibromatosis hyperpigmentation, and arachnodactyly like fingers (Figure 90) Marked vasomotor changes (blueness, sweating, blanching) can transiently occur during the acute paroxysms

The Ovaries

Primary Deficiency Increased pigmentation or sparse axillary and pubic hair (Figure 57) are noted on occasion

Menopause Acne rosacea chloasma kraurosis vulvae pruritus vulvae and ani, hypertrichosis (Figure 99), and keratoderma of the soles and palms (Figure 54) may all be related to the menopausal effects[112]

Arrhenoblastoma Acne, a masculine hypertrichosis (Figure 59) and other features of masculinization are very suggestive

Menstruation Exacerbations of certain existing dermadromes are prone to occur during the menses This is particularly true of urticaria various erythemas, herpes simplex, and pruritus with neurotic excoriations At times acne, angioneurotic edema or purpura (Figure 6) are also encountered

Pregnancy Regional hyperpigmentation, chloasma, hypertrichosis (Figure 99), abdominal striae (Figure 58), red palms, and cutaneous growths may be associated with pregnancy Other nonspecific herpetiform, purpuric (Figure 6), erythematous, and urticarial lesions have been observed

The Testes

Hypogonadism Hypogonadism in the male induces a female type of hirsutism The skin is usually thin yellowish, pale, and resists tanning The face shows fine wrinkles Gynecomastia (Figure 60) may also be present (the Klinefelter syndrome)

METABOLIC DISORDERS

(*Also see Group II*)

The Lipoidoses

Disturbed fat metabolism may induce the several xanthomatous dermadromes On occasion, they are also helpful in diagnosing certain con comitant liver and cardiovascular diseases (pp 76–79) [276-285] Some of the conditions that have features of local or generalized disturbances of lipid metabolism include the following

Xanthelasma A localized form of lipoidosis, xanthelasma is com monly associated with hypercholesterolemia (but not with essential hyper lipemia) Its appearance suggests the possible presence of underlying hepatic and cardiovascular (coronary) disorders Another hereditary xanthoma, *xanthoma tuberosum multiplex* (Figure 10), was described previously in this chapter (p 522)

Idiopathic Hyperlipemia of the Burger Grutz Type Also called hepatosplenomegalic lipoidosis this disorder is characterized by yellowish brown xanthomatous nodules papules or infiltrated plaques on the flexor surfaces of the larger joints the palms and soles, and the mucous membranes

Gaucher s Disease Patients with Gaucher's disease (kerasin lipoidosis) exhibit chloasma like spots bronzing ' (more pronounced on the face neck forearms and hands), pingueculae (Figure 97) purpura (Figure 6), and leg ulcers (Figure 89) Xanthomas are absent (p 78) [287]

The absence of pigmentation in the infantile form of Gaucher s disease contrasts with its presence in Niemann Pick's disease

Niemann Pick s Disease Niemann Pick s disease (sphingomyelin lipoidosis) is characterized by a yellowish brown wrinkled skin occasional xanthomata and black spots on the mucous membranes It primarily affects Jewish infants

Lipoid Proteinosis Lipoid proteinosis appears as verrucous, sclerotic nodular hyperkeratoses of the face, the extremities (in the form of plaques on the elbows and knees), and the mucous membranes Regressing lesions give a pitted pigskin like appearance to the skin Dental anomalies, hoarseness, rigidity of the tongue diabetes mellitus and derangements of the blood phospholipids may also occur in these patients [276 84]

The Parathyroids

Hyperparathyroidism Calcinosis cutis with single or multiple hard nodules and plaques over pressure points, especially on the arms, may be found either in this disease or in hypoparathyroidism (Figure 50)(p 23) Ulceration with extrusion of calcium deposits can occur

Hypoparathyroidism A dry, scaly, and pigmented skin together with scanty hair and transverse grooving of the nails are the important cutaneous features in this condition (Figure 30) Moniliasis (Figure 81) also frequently accompanies the juvenile form of this disease [13]

The Adrenals

Hyperadrenalism Hyperadrenalism is suggested by the acne, the facial plethora, the abnormal distribution of fat (i e , a large panniculus) and the reddish to purple abdominal striae that are characteristic of the Cushing syndrome There is frequently deep pigmentation in the folds overlying the joints of the hands Females may demonstrate hypertrichosis (Figure 59) along with a "buffalo hump' and male type of hirsutism (One should remember that while hypertrichosis is associated with acromegaly, adrenal hyperfunction or tumors, and ovarian dysfunction or tumors, it more often represents a familial trait) Darkened areolae occur in the male Purpura, acrocyanosis, brownish pigmentation, and poikiloderma like changes have also been observed

Hypoadrenalism Hypoadrenalism may be manifested by the addisonian hyperpigmentation (Figure 55) of the normally dark skin, the pressure or friction areas, the palmar creases the knuckles, scars, and the mucous membranes (Figure 56) Coexisting vitiliginous spots or numerous black freckles and moles are sometimes present There may be pubic and axillary alopecia (Figure 57)

Pheochromocytoma Pheochromocytoma has been associated with multiple neurofibromatosis, hyperpigmentation, and arachnodactyly like fingers (Figure 90) Marked vasomotor changes (blueness, sweating, blanching) can transiently occur during the acute paroxysms

The Ovaries

Primary Deficiency Increased pigmentation or sparse axillary and pubic hair (Figure 57) are noted on occasion

Menopause Acne, rosacea chloasma, kraurosis vulvae pruritus vulvae and ani, hypertrichosis (Figure 99) and keratoderma of the soles and palms (Figure 54) may all be related to the menopausal effects [11]

Arrhenoblastoma Acne a masculine hypertrichosis (Figure 59) and other features of masculinization are very suggestive

Menstruation Exacerbations of certain existing dermadromes are prone to occur during the menses This is particularly true of urticaria various erythemas, herpes simplex, and pruritus with neurotic excoriations At times, acne, angioneurotic edema or purpura (Figure 6) are also encountered

the involvement are the chest, the axillae and the groin There may be an associated loss of pigmentation, with the hair turning gray or red (Temporary redness of the hair has also been observed in ulcerative colitis [131e]) A "crazy pavement" patterning tends to follow clearing of the lesions

Hemochromatosis

This defect of iron metabolism is also referred to as pigmentary cirrhosis and bronze diabetes (p 60) The most striking dermal sign is a generalized melanoderma with light bronze to deep brown, black or slate-blue (argyria like) pigmentation resulting from the hemosiderin and hemofuscin depositions[15] (Figure 52) The blotches often resemble patches of dirt They tend to be more pronounced in the axillae the nipples the umbilicus, the genital region, scars, and in the parts exposed to light The oral mucosa lips, and conjunctivae may also become pigmented Coexisting loss of hair (Figure 57), xeroderma, pruritus, and purpura (Figure 6) are frequently noted[210]

Uremia

This state is characterized by a yellowish (urochrome) discoloration, edema of the eyelids, purpura, and pruritus due to the very dry skin (p 50) The ominous urea frost does not usually appear until the patient's condition is terminal Deep wrinkling of the forehead often reflects the patient's attempts to stay awake

Ochronosis

The pigmentation of the cartilaginous structures, ligaments tendons, nails and skin in this disease ranges in color from gray to blue brown, or black The ears and sclerae (Figure 49) are good sites to look for the pigmented spots[274] There is often a spotty pigmentation affecting the facial skin It is important to be cognizant of the associated and potentially severe arthritis, valvular involvement, and arteriosclerotic complications (p 75)

Gout

Hard, nontender nodules or tophi (Figure 51), especially on the external ears and at the juxta-articular sites, represent deposits of urates resulting from the faulty purine metabolism (p 74) Pruritus, hyperkeratosis of the palms and soles, and eczematoid or psoriatic eruptions may also be present

Diabetes Mellitus

Many dermadromes can occur during the course of diabetes, or they may antedate its clinical onset by as long as several years Urbach has stressed the concept of "skin diabetes" (hyperglycodermia without hyper-

The Hand Schuller-Christian Syndrome The dermadrome of the Hand Schuller Christian syndrome resulting from the generalized normocholesterolemic xanthomatosis consists of brownish red, papular, and sometimes scaly lesions in children and young adults (Figure 13) It may be associated with exophthalmos, diabetes insipidus, stomatitis, or any combination of these features (p 207) There may also be deep, sharply delineated, and ulcerated granulomatous lesions involving the skin of the inguinal, perianal, perineal, and vulvar regions, as well as the buccal mucous membrane "Eosinophilic granuloma of the skin" probably represents a related entity Other lesions noted include a bronze pigmentation, lipid infiltration of the eyelids, a hemorrhagic eruption, and flat yellow nodules [760-763]

Letterer Siwe's Disease Letterer Siwe's disease is an acute nonlipid disseminated reticuloendotheliosis in infants (Figure 14) It is also probably related to the Hand Schüller Christian syndrome and eosinophilic granuloma Cutaneous manifestations are almost always present They include petechiae, purpura, and a seborrheic type of eruption (p 208) [766, 767]

The Avitaminoses

These are broadly considered here because the vitamin deficiencies concomitantly participate in many other metabolic disturbances, such as thiamine deficiency in hyperthyroidism The reader is referred to a discussion of the avitaminoses in an earlier chapter (pp 42 to 44) Only the more characteristic dermadromes will be listed here

Avitaminosis A Most characteristic is a rough, follicular, hyperkeratotic, papular, and sometimes plaque-like eruption, particularly around the elbows, knees, and thighs The skin may be diffusely dry, scaling, pruritic, and pigmented The hair tends to be dry and lusterless

Avitaminosis B Single or combined vitamin B deficiencies are often suggested by the presence of an angular stomatitis, glossitis, cheilitis, keratitis, and perlèche in various combinations There can also be redness (rosacea), seborrheic dermatitis, scaling, fissuring, edema in the so-called wet type of beri beri, and pellagrous (Figure 46) or psoriatic areas A dull erythema and slight scaling process over the face that is sharply demarcated at the exposed areas of the hands, forearms neck, and sternal region characterize the pellagrin It must be appreciated that while ocular rosacea follows acne rosacea, it is usually precipitated by local infection rather than by riboflavin deficiency

Avitaminosis C Perifollicular petechial hemorrhages, ecchymoses (Figure 48), purpura, spongy receding gums, and gingival hemorrhages are suggestive of vitamin C deficiency There are *no* known dermadromes that result from D avitaminosis

Avitaminosis K Purpura (Figure 6) and petechiae or large ecchymotic areas (Figure 48) are commonly observed, especially over pressure sites on the torso

Kwashiorkor The dermatosis associated with severe protein starvation known as kwashiorkor consists of hyperpigmented and hyperkeratotic areas, and as such bears some semblance to pellagra [131b] The chief sites of

and neck, nail dystrophy, alopecia, seborrhea, hemorrhagic dermatoses, and exfoliation (p 402) [1173, 1174]

Systemic Intoxications

(Also see Groups II and XIII)

Only dermadromes of the systemic intoxicants are listed here, with few exceptions the allergic reactions have been omitted. The clinician must distinguish at times between cutaneous side reactions due to a wide variety of medications and drug allergy—the two terms actually not being synonymous. The following examples constitute drug induced cutaneous disturbances that are not the result of an allergy in the strict sense of the word: reactions due to the direct toxic effect of such agents as the heavy metals upon the tissues resulting in purpura and exfoliative dermatitis, reactions due to excessive dosage of the medication as in the case of atabrine pigmentation and ergotism and reactions stemming from idiosyncrasies such as iodism and bromism, which may bear little relationship to the amounts ingested. Some of the difficulty that arises in the diagnosis of drug allergies is related to the absence of demonstrable antibodies in most instances, and the little value of skin testing in such situations. This is often attributed to the role of a partial antigen or haptene that is exhibited by the drug in question.

In general, these toxic reactions to drugs and chemicals run an extremely variable gamut simulating many of the known dermatoses (p 511). Of greatest significance are the pruritic, erythematous exanthematous, poikilodermal and erythema multiforme-like (Figures 8 and 9) eruptions. Other common features include exfoliation and scaling hyperpigmentation jaundice hemorrhagic reactions (Figure 6) edema, alopecia, and keratoses (Figure 37).

Some classic associations are *Arsenic*—palmar and plantar keratoses (Figure 37) with hyperhidrosis erythema and pigmentation (p 68). These features are also seen in *mercury, bismuth manganese, and bromide* intoxications. *Silver*—bluish gray to deep bronze discoloration (argyria) (p 516). *Lead*—dark lead line at the gingival margin (Figure 38) (only when the teeth and gums are in very poor condition) (p 65). *Bismuth*—blue gum line and a brownish gray skin discoloration. *Mercury*—necrotic stomatitis (p 68). *Thallium*—loss of hair. *Bromides*—painful nodular, acneiform eruptions (Figure 36) (p 64). *Gold*—gray pigmentation over the exposed areas resembling argyria. *Iodides*—pustules and papules (p 404). *Phenolphthalein*—macular sometimes bullous, purplish brown spots. Certain *coal tar derivatives* are prone to induce erythema nodosum (Figure 5), or purpuric (Figure 6), petechial, agranulocytic and other hemorrhagic rashes.

Liver and Biliary Tract Disorders

(Also see Group III)

Jaundice, the most characteristic dermadrome in this group of diseases can range from a slight yellowish icteric tint, to a lemon, greenish

glycemia or "cutaneous glycohistechia") as a result of his studies on the fasting skin sugar levels in patients with *recurrent or chronic dermatoses* which proved to be resistant to nondiabetic therapy[1401] These include a dry, hypercarotenemic skin, pruritus, vulvitis, periorificial eczema, xanthoma diabeticorum (Figure 11), other xanthomas (Figure 10), the mycoses, ulcerations, pyodermas, furuncles, carbuncles, necrobiosis lipoidica diabeticorum (Figure 12), and gangrene due to trophic or vascular disturbances (p 70) [1382 1383 1388] Most of these tend to recede once the diabetes is controlled Spontaneous blebs occurring without apparent cause (particularly on the feet) are noted on a number of occasions in diabetics *This phenomenon is related in large measure to the coexisting vascular and* neurologic lesions[1402] The apparent high association of Kaposi's sarcoma and diabetes mellitus was previously cited (p 526)[1400]

Porphyria

Defective porphyrin metabolism may be reflected by the presence of brownish, purple-fluorescing pigmented spots—usually over the exposed areas—which are photosensitive (Figure 17) (p 61)[15 220] Hyperpigmen*tation is often patchy and surrounded by areas of vitiligo* The history of red hair turning dark or black, or of gray hair darkening is suggestive of this disease In *porphyria congenita erythropoietica* having its onset in early childhood, the teeth are apt to stain red to brown (Figure 16)

Amyloidosis

This disturbance of metabolism produces yellowish, shiny, translucent, waxy nodules in the skin particularly about the nose, eyes mouth, and mucocutaneous junctions These small lesions can resemble lichen planus or the xanthomas A significant erythema may occur In primary systemic amyloidosis pruritus is usually absent, but macroglossia (Figure 35), petechiae and ecchymoses (Figure 48) are often present (p 59) A localized form of amyloidosis is encountered in which the cutaneous plaques *become pruritic verrucous and lichenified* (Figure 98)[202 204]

Hypogammaglobulinemia

There are a number of possible dermatologic manifestations of hypogammaglobulinemia These include recurrent pyodermas furunculosis, cellulitis, generalized postvaccination vaccinia, moniliasis (Figure 81), pyoderma gangrenosum, purulent conjunctivitis, and even exfoliative dermatitis (p 145)[4,5 6 7]

Hypervitaminosis A

A number of cutaneous manifestations can occur *in this condition* (Figure 39) These consist of an intense pruritus, a follicular hyperkeratosis, dry and cracked mucous membranes hyperpigmentation of the face

All these lesions tend to undergo exfoliative, hemorrhagic, necrotic, and ulcerative changes

Hodgkin's Disease

These dermadromes are similar to those encountered in leukemia, except for the fewer specific lesions (p 181) [651] Pruritus, prurigo (Figure 26B), petechiae exfoliation, and xeroderma are the most common The specific dermatoses are mainly widespread papular rashes, tumefactions (Figures 24 and 26A), and persistent ulcerations, especially over the lymph glands While three phases of mycosis fungoides are classically described (i e , the premycotic or erythematous stage the plaque or infiltrative stage, and the tumor stage), note must be taken of the frequent divers patterns that are encountered in practice wherein one or more of these phases may be absent The so-called *Spiegler Fendt sarcoid* is not due to sarcoidosis but is generally regarded as a manifestation of the lymphoblastomata The localized form may persist for long periods as red *dish or purplish discrete, elevated lesions* or plaques with a firm con sistency The face is a common site

Lymphosarcoma

The "Eleven P s" apply in this disease Specific metastatic red to brownish nodules (Figure 24) are the most characteristic lesions encountered The nonspecific dermadromes include pruritus, urticaria herpes zoster (Figure 18), dermatomyositis (Figure 71), papules, vesicles, purpura (Figure 6), and ecchymoses (Figure 48) Scaly, eczematous or psoriatic eruptions which may ulcerate have also been observed

The Anemias

Pallor is the classic clue to anemia Pallor of the palmar creases noted with the skin stretched—particularly when contrasted with normal palms adjacent—is an especially valid sign The ear lobe offers another advantageous site to detect anemia

In *hypochromic anemia*, the skin may be a yellowish green Other sig nificant signs include perlèche a smooth shiny tongue, ecchymoses, koilonychia (due to softening of the nails) intertriginous erythema, ulcers of the lower legs, and premature graying of the hair The *Plummer Vinson syn drome* consists of dysphagia and hypochromic anemia, along with pallor, an atrophic glossitis, atrophy of the oral and pharyngeal mucosae and thin or spoon nails The readiness with which an associated gastrointestinal malignancy might be overlooked if the clinician satisfies himself with this diagnosis was pointed out previously (p 189)

☛ In *pernicious anemia*, there is a dry icteric yellowish waxy and delicate skin (Figure 3) with diffuse or pellagrous pigmentation especially on the torso, the dorsa of the hands and the palmar creases A bright red smooth, atrophic glossitis (particularly at the tip and edges) with occasional ecchymoses is often noted Vitiligo may be pronounced, espe-

brown, or purplish discoloration A greenish to bronze jaundice is seen in prolonged biliary obstruction, a greenish jaundice in liver necrosis, a yellowish-blue jaundice in cardiac insufficiency with cyanosis, and an orange or saffron jaundice with hepatitis There is also a tendency to pruritus, urticaria, xanthomatous lesions (Figures 10 and 11), chloasma like "liver spots," petechiae, purpura and ecchymoses (Figures 6 and 48) Porphyria, clubbing of the fingers and toes, and osteoarthropathy may develop

Cirrhosis of the Liver A yellow or greenish skin, icterus of the sclerae, and pruritus are common in portal cirrhosis, as are the vascular lesions ("spiders"), or stellate telangiectases above the nipple line (p 85) (These spider angiomata may be seen not only in avitaminosis, Osler's disease, hyperthyroidism, lupus erythematosus, and other pathologic states, but also in healthy individuals and in pregnant women) Impaired estrogen metabolism contributes in large measure to the gynecomastia, enlarged nipples (Figure 60), partial axillary (Figure 57) and pubic alopecia in men, and telangiectases (Figure 41) The palmar erythema (referred to as "liver palms") and spider nevi often fluctuate with the severity of the liver disease Dilated veins of the thoracic and abdominal walls are significant signs as is a bleeding diathesis (Figure 48)

In *biliary cirrhosis*, severe jaundice and widespread xanthomata (Figures 10 and 11) may occur The dermadromes of *hemochromatosis* were described under "Metabolic Disorders' in this chapter (p 535)

Hematologic Diseases

(Also see Groups VI, VIII, and IX)

Bluefarb[1017] has set forth the following "Eleven P's" as an aid in recognizing the dermadromes of both the leukemia lymphoma group and other internal cancers (1) pallor (Figure 3), (2) pruritus, including urticaria, (3) prurigo-like papules (Figure 26B), (4) pyoderma, (5) pigmentations of diverse types, including acanthosis nigricans (Figure 1), (6) pemphigoid or bullous lesions (7) pityriasis rubra or exfoliative dermatitis, (8) posterior ganglionitis or herpes zoster (Figure 18), (9) purpura (Figure 6), petechiae, and other vascular phenomena, (10) poikilodermatomyositis, and (11) phlebitis (Figure 42)

Leukemia

Various combinations of the 'Eleven P's' occur, although none is characteristic (p 181)[651] Pruritus with various rashes (Figures 25 and 26) is perhaps the one most commonly encountered Purpura (Figure 6), urticaria, erythroderma, prurigo lymphatica (Figure 26B), herpes zoster (Figure 18), other vesicular or bullous eruptions, and a painful, spongy hemorrhagic gingivitis (Figure 29) with a membrane over the gums are significant nonspecific dermadromes Specific infiltrations range from the exanthematous rashes (Figure 25) to large cutaneous tumors (Figure 26A)

inflammatory, pigmentary, proliferative, atrophic vascular, or nevoid characteristics Kierland has reviewed the cutaneous manifestations of the leukemias and the lymphomas [651] The following dermadromes are cited as the more important of these cutaneous neoplastic manifestations

1 An ashen gray pallid color or a yellowish tinted, thin translucent, wrinkled skin (Figure 3) can be produced by an associated iron deficiency *anemia*

2 *Pruritic and pruriginous features* (Figure 26B) are most striking in Hodgkin s disease and in the leukemias

3 *Urticaria* with chronic generalized pruritic wheals—in the absence of a frank allergic background—occasionally heralds an underlying neoplasm

4 The light brown to deep blue black round, oval, or blotchy *melanotic spots* (Figure 2) of the oral mucosa, perioral and periorbital regions, fingertips and toes in dark complexioned persons strongly suggest precancerous intestinal polyposis (p 124) [1 50 1 5] Several authors have been impressed by the association of malignant internal tumors in early adult life with *unilateral nevi* which were present since birth or childhood *Other pigmentations* may portend metastatic melanoblastoma leukemia ("l homme rouge), and the lymphomas

5 Thickening of the skin accentuation of the number and depth of the folds about the face and scalp rough palms, hypertrophy of the thenar and hypothenar eminences, clubbed fingers hippocratic nails and thickening of the joints (*pachydermoperiostitis*) may indicate a bronchogenic carcinoma [1037 1038]

6 The darkly pigmented plaques of *acanthosis nigricans* (Figure 1B) may appear as verrucous, papillomatous or nevoid lesions They tend to occur in the body folds of the axillary nuchal, periumbilical and genitocrural regions This dermatosis is often an ominous sign of adenocarcinoma (pp 322 and 513) A nonmalignant type of this lesion (Figure 1A) also occurs in adolescence [1018]

7 Instances of acute and subacute *dermatitis* with epidermal necrosis, plantar and palmar hyperkeratosis, and hyperpigmentary features (Figures 20, 46 and 54) are continually being reported in association with a wide variety of neoplastic diseases [1019]

8 An *ichthyosiform atrophy* of the senile ichthyosis type may be the principal feature of Hodgkin s disease This dermatosis has exhibited remarkable remissions following therapy [650]

9 Inflammatory reactions of the skin subcutaneous tissue and underlying muscle (*dermatomyositis*) (Figure 71) are frequent concomitants of internal cancer, especially of mammary or ovarian origin (p 308) [956 957] Poikiloderma (Figure 92) can be superimposed (*poikilodermatomyositis*), or it may be transformed into one of the leukemias or lymphomas

10 *Exanthematous rashes erythema multiforme pityriasis rubra exfoliative erythroderma* or generalized polymorphic *erythematous eruptions* consisting of various papular vesicular, bullous (Figure 8), and scaly lesions are significant neoplastic dermadromes So is the constantly changing reddish wavy, gyrate serpiginous wood grain like eruption known as *erythema gyratum repens migrans* This entity is most often encountered in

cially during the summer Cheilosis, stomatitis, and perlèche are additional manifestations of pernicious anemia (p 190)

Sickle cell anemia is suggested by the finding of punched out ulcers (Figure 89) above the ankles in Negroes (p 195)

Polycythemia Vera

Polycythemia vera presents the classic dermadrome of a generalized, chronic, purplish red plethora, especially of the hands and face A pruritic papular rosacea (or acne urticata) involving the face and the midchest is not uncommon Purpura (Figure 6), marked dermographism, telangiectasia (Figure 41), papular hemangiomata, and purplish macroglossia with atrophic papillae are also indicative of the primary disorder The skin occasionally exhibits hemosiderin pigmented reddish or brown spots Arterial disease with a thrombotic tendency (Figure 42) and ulceration or gangrene of the legs is a frequent complication Intense pruritus after a bath occurs in one third of these patients (p 188)[680] Clubbing of the nails (Figure 34) is rare in primary polycythemia ("red with a little blue"), in contrast to its incidence in secondary polycythemia ("blue with a little red")

The Hemorrhagic Diseases

Purpura (Figure 6), petechiae, and ecchymoses (Figure 48) are the *important dermadromes in this group*

Hemophilia Extensive ecchymoses and hematomata that result from minor bruises characterize true hemophilia petechiae are rare however

Hereditary Hemorrhagic Telangiectasia (Osler s Disease) The onset before the age of twenty years of persistent, increasingly numerous, and grouped telangiectases (Figure 41) involving the skin the tongue, or the circumoral and buccal mucous membranes is typical There may be small, dark red, hemangiomatous, nonblanching papules All the lesions bleed easily (p 222)

Thrombocytopenic Purpura Easy bruising and large numbers of spontaneous purpuric spots (Figure 6) with petechiae and extravasations over the pressure areas frequently appear This disorder often manifests itself first in the lower extremities and then becomes generalized

Nonthrombocytopenic Purpura (Henoch-Schonlein) Purpura (Figure 6) and urticaria are the most characteristic eruptions In addition, recurrent crops of erythema nodosum (Figure 5) or erythema multiforme-like lesions may cover the legs (p 224) Other serious hemorrhagic diseases with prominent purpuric features include *purpura fulminans* and the *Waterhouse Friderichsen syndrome* (Figure 79) (p 159)

Neoplastic Diseases

(Also see Groups VI and XI)

Curth, Bluefarb and others have demonstrated that the nonspecific neoplastic dermadromes can occur singly or in various combinations, with

The designation of *neurocutaneous syndromes* (congenital ectodermoses, phakomatoses) refers to the following four entities

1 *Von Recklinghausen's neurofibromatosis*, consisting of neurofibromatous tumors in the skin and along nerve trunks (Figure 28), alopecia, café au lait spots, epilepsy, and bone lesions including scoliosis (p 383) [1143] [1144] The tumors may be sessile, nodular, or plexiform Only rarely do they undergo malignant degeneration A 'forme fruste" might be suspected by the finding of six or more café au lait spots, each one exceeding 1 5 cm in its broadest diameter Fewer such lesions are required, however, if a family history of the disease exists [1145] The demonstration of neurofibromas *on the skin in a patient with an unexplained paralysis or sensory* derangement could indicate the presence of a similar nerve tumor in the cauda equina or some other area within the spinal canal

2 *Tuberous sclerosis*, characterized by adenoma sebaceum (firm, yellowish, waxy papules over the middle third of the face and nose) (Figure 67), epilepsy, mental retardation various pulmonary and osseous abnormalities macular atrophy, and a wide variety of other dermatoses (p 426) The latter include subungual and periungual fibromas other tumors nevi (pigmented hairy, vascular) pigmentation disturbances (café au lait spots diffuse bronzing, vitiligo), changes in the nails ichthyosis, and hyperkeratoses (especially of the palms and soles) [1358] This condition has at times been present along with neurofibromatosis in the same patient

3 *The von Hippel Lindau disease*, in which angiomatosis is associated with arteriovenous communications in the retina and skin telangiectases (p 382) [114-]

4 *The Sturge Weber Dimitri syndrome* (encephalotrigeminal angiomatosis) characterized by cutaneous 'port wine' nevi overlying the superior and middle branches of the trigeminal nerve (usually unilateral), convulsive seizures, hemiplegia, unique intracranial calcifications, and mental deficiency (Figure 65 and p 382)

The skin over areas of *impaired innervation* tends to become atrophic and may even ulcerate Sensory and pigmentary changes also occur *Cord lesions* due to tabes dorsalis diabetes mellitus and syringomyelia often cause trophic ulcerations and localized pigmentations

Spina bifida occulta may often be suspected by a circumscribed patch of hair over the spinal column *Organic brain damage* can be reflected in the form of unilateral sweating, edema dryness, scaliness of the skin and pigmentary changes Purpura (Figure 6) the "fur cap hair line, and diffuse hypertrichosis (Figure 59) also occur in the presence of central nervous system damage

Idiopathic epilepsy has been associated with urticaria, vasomotor instability, petechiae about the head and neck, chloasma and pachydermal folds of the scalp The latter manifestation, known as cutis verticis gyrata is also seen in *microencephalic idiocy*

It is most important to recognize and treat the *shoulder hand syndrome* in its early phases before the trophic and vasomotor changes have resulted in permanent atrophy of muscle, bone, and the subcutaneous tissues This complication is most apt to occur following a hemiplegia or an acute myocardial infarction (p 221)

lung and breast malignancies [1394] It has been considered as a possible allergy to some "carcinotoxin"

Erythema multiforme has ensued from one to twenty one days following *deep x ray or radium therapy for malignant tumors This is presumably* due to the absorption of the released toxic products resulting from the induced cellular degeneration [1394] The same association has also been observed in the case of *herpes zoster* and *dermatitis herpetiformis*

11 Herpetiform eruptions, including *herpes zoster* (Figure 18) and *dermatitis herpetiformis* (Figure 20), and *the pyodermas* are associated with malignancy often enough to suggest a possible underlying background [516, 651, 1017] A gangrenous, hemorrhagic and generalized herpes zoster might simulate pemphigus This form of the diesase, in particularly, should immediately raise the possibility of an underlying lymphoma, leukemia, or myeloma

12 A variety of neoplasms, including kidney tumors, rhabdomyoma *of the heart, and subungual and periungual fibromas of the digits, bear an* association with *adenoma sebaceum* (Figure 67) [1388] This is a nevoid disorder which is characterized by the presence of firm, yellowish, waxy papules over the middle third of the face in the area of the inner cheeks and nose (p 426)

13 *In metastatic functioning carcinoid tumors of the small bowel,* the earliest manifestations may be apparent as a transient and changing flushing of the skin, especially over the face and neck (p 347) [1070, 1074] These vasomotor phenomena later mingle with patches of cyanosis and white blotches They have been confused with those resulting from ovarian insufficiency (Figure 7)

14 Patients with *poikiloderma vasculare atrophicans* tend to develop either mycosis fungoides or another one of the lymphoblastomata [650] The "x ray skin" is dry, pruritic and atrophic It may also exhibit pigmented spots, telangiectases, ulcerations, and photosensitivity (Figure 92)

Disorders of the Nervous System

(Also see Group XII)

Neurologic Disorders

The multiplicity of disorders in which both cutaneous and neurologic counterparts are found underscores the embryologic fact that the skin is actually an exposed part of the depressed nervous system (or conversely, that the central nervous system is a depressed part of the skin) Beerman has ably reviewed these entities, among which can be listed the Hand Schuller Christian disease, leprosy, the Ramsey Hunt syndrome, lupus erythematosus, polyarteritis pellagra, kernicterus Gaucher's disease, gargoylism, pseudoxanthoma elasticum, mongolism, herpes simplex, the ectodermal dysplasias, and sarcoidosis [1403] Reference was made earlier in this chapter to the many types of intracranial disease (i e, Schilder s disease, encephalitis, ependymoma of the third ventricle, hepatolenticular degeneration, pituitary tumors with normal adrenals, and even schizophrenia) that may be associated with generalized pigmentation [1392]

The Collagen Disorders

In view of the considerable impact of the dyscollagenoses upon diagnostic medicine in recent years, their cutaneous manifestations will be given a somewhat more detailed emphasis in this chapter (Also see Group X)

Systemic Lupus Erythematosus

The characteristic eruption or its equivalent dermadromes are present in a large percentage of these patients The former is a sharply demarcated erythematous rash that eventually involves the malar region and the bridge of the nose (the so-called "butterfly" distribution) These lesions are usually indurated elevated, and covered by silvery scales which overlie the atrophic dilated follicles with follicular plugs The erythema can be seen to also affect the V shaped areas of the exposed neck and upper chest Long standing, minute scattered areas of telangiectasia may be noted (Figure 68)

Other skin manifestations of lupus include focal or diffuse pigmentation, petechial hemorrhages, purpura indurated nodules at the ends of the fingers and toes urticaria, a patchy or total alopecia intense pruritus and the Raynaud phenomenon One variant of lupus, the Senear Usher syndrome, consists of an extensive pemphigoid bullous eruption along with the aforementioned erythema affecting the face and neck

A history of overexposure to sunlight or to ultraviolet radiation preceding the onset of symptoms is suggestive of lupus and merits an L E cell test It must be appreciated that the current classifications of lupus are arbitrary, and that many transitions exist between the localized discoid form the generalized form and the classic systemic symptom complex (pp 304 to 307)[9 8 931 936]

Polyarteritis (Periarteritis Nodosa)

A similarly high incidence of dermadromes may be encountered in this disorder (Figures 40 and 69) Of these attention is directed to the occurrence of petechial hemorrhages, purpura Raynaud s phenomenon localized areas of skin necrosis (even suggesting embolic phenomena), urticaria, erythema nodosum like or erythema multiforme-like eruptions and crops of painful subcutaneous nodules or papules (p 307)[943 945] The nodules and papules are encountered chiefly along the course of a superficial artery on the trunk and extremities Remissions and exacerbations do occur The manifestations of polyarteritis occasionally have been found to mask those of a secondary and concomitant acute porphyria hepatica[992]

Dermatomyositis

The typical cutaneous lesion often begins as a purplish discoloration of the eyelids It then tends to progress in the form of a heliotropic swelling involving the circumorbital area and of a symmetrical violaceous erythema

The "diencephalic blush" in the *diencephalic syndrome* resembles a histamine reaction. Marked vasomotor changes of the skin and a very labile blood pressure occur concomitantly.

Incontinentia pigmenti (Bloch Sultzberger) is one of the cutaneous manifestations of a congenital and possibly a familial disorder that affects various structures of ectodermal and mesodermal origin, including the autonomic nervous system (p 425).[157, 158] There is a striking and bizarre arrangement of pigmented macules in "chocolate brown designs," including whorls, patches, "fountain spray" patterns, and spidery forms. It is at times preceded by inflammatory lesions of either a vesicular or bullous nature. Alopecia, delayed dentition, osseous deformities, corneal opacities, cataracts, and a variety of neurologic phenomena (viz, spastic paralysis, strabismus, epilepsy, microcephaly, mental deficiency, optic atrophy) have also been observed in this disorder.

In a patient with severe headache, facial pain and an oculomotor palsy, the finding of unilateral or bilateral proptosis, dilated facial veins, and a dusky red discoloration suggests the probability of a *cavernous sinus thrombosis* (Figure 66). The presence of a facial furuncle that may have initiated the difficulty adds further validity to this diagnosis.

The Psychoneuroses

Obermayer has aptly entitled his fine volume on the subject as "Psychocutaneous Medicine."[1409] The psychologic backgrounds that can contribute to the desire to scratch are legion. The more commonly recognized ones include the following: displaced sexual gratification, the need for self excoriation to satisfy masochistic impulses, the relief of tension that is incident to the act of scratching, and the expression of various emotions such as shame, guilt, and exhibitionism.[1383, 1409]

Various disorders of the hair may be striking. These can appear as alopecia areata in the anxiety states, and as alopecia totalis in the depressions. Included among the other common dermadromes are a dry skin, a dry oral mucosa, vasomotor instability, acrocyanosis, urticaria, dermatitis factitia (due to inordinate compulsive scratching, picking, nail biting, hair plucking or trichotillomania, eczema, and self inflicted chemical or physical trauma). Psychogenic factors in functional and fatigue states can sometimes be deduced from the presence of localized pruritus, formication, neurotic excoriations, urticaria, angioneurotic edema, localized hyperhidrosis, atopic eczema, and pompholyx.

Neurocirculatory asthenia is associated with excessive palmar sweating, a pronounced tremor, and cold, mottled, cyanotic fingers which are usually tobacco-stained or nail bitten. Other psychosomatic phenomena encountered in states of autonomic imbalance include dyshidrosis, vasomotor instability, and fluctuations in the skin temperature.

In addition to the usual changes in neurodermatitis, *neuronychia* may be one of the few somatic manifestations of severe anxiety and emotional disease. Superficial pitting, thinning, or splitting are observed, along with separation of the nails from their bed.

on the thighs they have also been observed on the extremities and the trunk The individual nodules are generally less than 1 cm in diameter but coalescence into larger lesions is commonly encountered (Figure 73)

Poor healing at the site of a biopsy, depression and pigmentation of the skin in the area of previous involvement remissions of the individual attack after a month or longer, and the concomitant appearance or subsidence of fever with the cutaneous exacerbations and remissions, respectively, are characteristic of this disorder (p 309)[970, 971] While the nodules do not as a rule break down or ulcerate, local suppuration can occur, leading to drainage Some difficulty might arise in differentiating this disorder from erythema nodosum and nodular vasculitis Enlargement of the liver and the spleen also occur with moderate frequency in nodular panniculitis

Rheumatic Fever, Rheumatoid Arthritis and Erythema Nodosum

These are discussed elsewhere in this chapter The following additional entities, which also involve systemic disturbances in the connective tissue of the body, will be briefly enumerated for the sake of completeness—even though most authors do not refer to them in discussions of the collagen disorders

Elastica Disease ("Hereditary Elastodystrophy")

Pseudoxanthoma elasticum the basic dermadrome is characterized by the presence of bilaterally symmetrical skin lesions which are usually noted in the neck and the flexural folds of the axillae, elbows, knees, and groin (Figure 74) They appear as cream colored to orange papules ('birth marks') under the cutaneous lines and vary from a pinhead to a large pea in size Long wide yellowish striae may be found on the sides of the neck The development of a yellowish lesion at the sites of trauma by a corset or a tight belt is often the initial clue to the presence of elastica disease The association of this eruption with vascular phenomena, hypertension, separation of the retina and a hemorrhagic diathesis was previously described in the text (p 314)[986-988]

The Ehlers Danlos Syndrome (Cutis Hyperelastica)

The various "formes frustes of this disorder may be very confusing to clinicians working in many fields and also to pathologists In its fully developed state it is characterized by cutaneous hyperlaxity, and by marked friability of the skin and blood vessels, with their subsequent splitting and the formation of hematomas and molluscous pseudotumors (p 314)[989]

The preservation of the elasticity of the skin in cutis hyperelastica contrasts with the condition known as cutis laxa where the skin has no elasticity hangs in folds and does not return to its previous status after being stretched Other defects that are described in association with the Ehlers-Danlos syndrome include clubfoot, dental anomalies, and cardiac changes

affecting the face, neck, and trunk (Figure 71) Peripheral vascular complications and cutaneous eruptions resembling erythema multiforme or erythema nodosum have also been observed [953 955] It can closely resemble scleroderma clinically A number of conditions recurrently require consideration in the differential diagnosis of dermatomyositis These include lupus erythematosus, scleroderma, scleredema, photosensitivity reactions, erysipelas, trichinosis, and the many causes of polyneuritis

As is the case in disseminated lupus erythematosus, the involvement of the skin over the underlying inflamed muscle groups and subcutaneous tissues may be either very late in appearing, or it may even be absent

Once again, the high association of this condition with various malignant diseases is stressed (p 308) [956 957] In the *poikilodermatomyositis* that often accompanies an underlying malignancy, the flexures and axillae are favored, while the face may be spared In contrast to the mottled edema and facial erythema found in dermatomyositis, pigmentation, telangiectasia, and reticulation occur in this condition—usually without the scleroderma or Raynaud's phenomenon

Scleroderma

Whereas the focal indurated forms of this entity (morphea) on the neck, trunk, or extremities are not likely to progress, diffuse scleroderma is another matter The latter disorder produces an edema that is followed by patchy atrophy and contraction of both the skin and subcutaneous tissues This results in the very characteristic hard, waxy, pigmented, and wrinkle-free appearance of the affected skin (Figure 70) Telangiectasis, Raynaud s phenomenon, alopecia, trophic ulcerations, calcinosis of the muscles and soft tissues, deformities of the fingernails, and severe cyanosis may coexist (p 309) [802 959 962] The patient with circumscribed scleroderma should be constantly reassured that there is no danger of systemic involvement

Scleredema Adultorum (Buschke's Disease)

This benign dermatosis can also simulate scleroderma, but it usually terminates in spontaneous recovery within several months There is a diffuse, nonpitting edema that affects the face neck and upper part of the chest (Figure 72) It usually follows an upper respiratory infection The infrequency with which the hands and feet are involved is in striking contrast to the scleroderma process The skin may be pale and indurated, but usually maintains its normal appearance without pigmentation or depigmentation (p 309) [969]

Weber-Christian Disease (Relapsing Febrile Nodular Nonsuppurative Panniculitis)

This disease is probably one of the more benign of the dyscollagenoses The subcutaneous lesions are usually raised, tender, freely movable, and associated with an erythema of the overlying skin Although most common

on the thighs, they have also been observed on the extremities and the trunk The individual nodules are generally less than 1 cm in diameter, but coalescence into larger lesions is commonly encountered (Figure 73)

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Epidermolysis Bullosa

This is a hereditary disorder in which deficiencies or absence of elastic fibers of the skin result in increased cutaneous vulnerability Although most of the cases begin in infancy, the so-called acquired form has been noted to become manifest for the first time during adult life, in these instances, it may be associated with porphyria The severity of this dermatosis can range from occasional bullae following trauma to a severe type in which the vesicles, bullae, and epidermal cysts are accompanied by loss of hair, dystrophy of the nails, microcephaly, leukoplakia, and carcinoma

The vulnerability of the skin to trauma in epidermolysis bullosa is demonstrated by the occurrence of bullae and severe dystrophic changes at the sites of the greatest trauma, viz , the pressure points on the feet, the knuckles, the elbows, and the knees On occasion, some difficulty might arise in differentiating the dystrophic form of epidermolysis bullosa from drug eruptions and the other major bullous diseases (viz , dermatitis herpetiformis, pemphigus, and erythema multiforme)

It is pointed out that simple epidermolysis bullosa tends to run a chronic course which is benign with reference to the patient s general health *Furthermore there are undoubtedly a large number of individuals* with latent epidermolysis bullosa whose disorder is manifested as "chronic ringworm" of the nails, or as "blistering" of the feet The latter is usually attributed to the degree of the person's activity or to improperly fitted shoes

Infectious Diseases

Only a brief segment of those infectious diseases whose cutaneous manifestations have proved to be of unique interest and importance to clinicians will be cited here The majority of the commoner infectious diseases, the exanthemata and the mycoses have been omitted as categories of diseases whose dermadromes are too well known to merit further emphasis in this book The reader is also referred to Groups IV and V of the text

Tuberculosis

There has always been much confusion concerning the classification of cutaneous tuberculosis The one set forth by Pillsbury, Shelley, and Kligman which follows is helpful in the clinician's orientation [1383]

True cutaneous tuberculosis (i e the lesions contain tubercle bacilli)

A Primary tuberculosis (patients may be tuberculin negative in the early phases)
   1 Primary implantation tuberculosis producing a tuberculous chancre and part of the primary complex on the skin
   2 Miliary tuberculosis of the skin from hematogenous dissemination
B Secondary tuberculosis (the organisms may be difficult to isolate in this reinfection type lesion)

1 Lupus vulgaris
2 Tuberculosis verrucosa cutis
In both of these forms, the tubercle bacilli have been inoculated into the skin from either external or internal sources
3 Scrofuloderma (the skin involvement results from an extension of an underlying focus in either the bone or the lymph nodes)
4 Tuberculosis cutis orificialis (these are primarily lesions of the mucous membranes which extend onto the skin at the mucocutaneous junctions of the nose mouth, anus, and genitalia)

Tuberculids (i e , the lesions represent an allergic reaction, but contain no tubercle bacilli)

A Papular forms
1 Lupus miliaris disseminatus faciei (purely papular) (Figure 75)
2 Papulonecrotic tuberculid (papules with necrosis)
3 Lichen scrofulosorum (follicular papules or lichenoid papules)
B Granulomatous, ulceronodular forms
1 Erythema induratum (nodules or plaques that subsequently ulcerate) (Figure 77)

Generalized excessive sweating and brilliant cheeks are commonly observed in pulmonary phthisis *Lupus vulgaris* consists of small "apple-jelly nodules (not pathognomonic however) in discrete to large coalesced patches with scarring *Scrofuloderma* (tuberculosis colliquativa) is characterized by a cervical lymphadenopathy with overlying ulcers and fistulae *Tuberculids or lichen scrofulosorum* are occasionally seen on the backs of children or young adults The eruptions may be pink to brown, follicular, papular and scaly or they can appear as bluish red pruritic and papulonecrotic lesions on the arms and legs with central necrosis

Erythema induratum (Figure 77) consists of persistent hard round well defined deep nodules with bluish red surfaces The latter entity (also known as Bazin s disease) is typically found over the lower calf area and differs from erythema nodosum by its insignificant pain its ulcerations and its chronicity

Syphilis

The cutaneous ramifications of primary, secondary and tertiary syphilis are too legion to enumerate here It is sufficient to restate the dictum that all unexplained ulcers rashes, tumors and lesions in *any* area of the skin—particularly if they present the triad of induration chronicity and a satellite adenopathy—should be regarded as luetic until proved otherwise (Figure 78) This original great mimic is still very much a problem, notwithstanding the availability of penicillin (p 154)

Meningococcemia

This infection is usually unknowingly treated before the characteristic eruption occurs Crops of skin lesions appear over the extremities, the palms the soles, and the mucous membranes (Figure 79) They may con

sist of macules, papules, nodules, vesicles, petechial hemorrhages, and purpuric spots in which necrosis often takes place (p 158)[52, 573]

Herpes Simplex and Herpes Zoster

These were discussed earlier in this chapter (p 522) In the case of the former, the finding of the characteristic multinucleated giant cells and intranuclear inclusion bodies in skin biopsies helps to differentiate it from variola (p 789) (See Section X of Part II)

Diphtheria

Attention is specifically directed to the problem of acute or chronic cutaneous diphtheria in the warmer climates Lesions of many descriptions have been observed, including the eczematoid, impetiginous, vesicular, pustular, bullous, ulcerative, and gangrenous forms The diphtheritic ulcer is typically punched out with hard, rolled, and elevated edges (Figure 88) It is often covered by a leathery membrane which must be removed before local therapy can be successful The incidence of both neuritic and cardiac complications from cutaneous diphtheria is very high (p 160)[58] Not only can diphtheria cutis simulate the various other ulcerative bacterial infections of the skin (*vide infra*), but it may complicate a wide variety of pre-existing inflammatory diseases, such as eczematous dermatitis

Gonococcemia

A variety of skin lesions were noted in the pre-antibiotic era These included a maculopapular eruption, purpura, erythema multiforme (Figure 8) erythema nodosum (Figure 5) and keratosis blennorrhagica (Figure 80 and p 159)[577] The latter also frequently accompanies Reiter's disease

Moniliasis (Candidiasis, Oidiomycosis, Thrush)

Clinicians should be aware of the following causes for symptomatic moniliasis (Figure 81) in its various localized and generalized forms diabetes mellitus, antibiotic therapy, obesity, the avitaminoses alcoholism, hyperhidrosis, and idiopathic hypoparathyroidism[13, 511, 512] Erosio interdigitalis blastomycetica, chronic paronychia and onychia, and candidial vulvitis or vaginitis are particularly valuable clues to the presence of a latent diabetes mellitus

Erythema Multiforme Exudativum

The numerous variants of the "mucocutaneous ocular syndromes" are probably due in large measure to this disease The Stevens Johnson (Figure 4) and Reiter's syndromes are the ones best known This disorder should be actively considered in the presence of a severe stomatitis urethritis, conjunctivitis, keratoderma blennorrhagica, and balanitis circi-

nata, especially when these manifestations are accompanied by an explosive inflammatory polyarthritis [585, 586] The various dermatoses produced may resemble those of rheumatic fever (erythema marginatum), erythema nodosum, lupus erythematosus, pemphigus, drug sensitivities, the exanthemata (particularly "chicken pox that lasts too long"), and erythema multiforme

Dermadromes of Other Specific Infections

Brief résumes of the unique skin eruptions of other specific infections are included in the following listing

Rocky Mountain Spotted Fever A maculopapular exanthem initially appears on the wrist, ankles, palms soles and forearms, and later becomes hemorrhagic, the mucous membranes may be involved, especially in severe cases, skin necrosis cyanosis, and gangrene of the digits have also been observed (p 162) (Figure 40)

Epidemic Typhus Fever The dermatosis is similar in most respects to that of Rocky Mountain spotted fever, except that the rash is classically first noted in the axillary folds and on the trunk

Typhoid Fever The "rose spots" (Figure 76) usually appear on the lower chest or abdomen, they are not hemorrhagic (p 163)

Rickettsialpox There is early vesiculation of the maculopapular rash which may involve the oral cavity but spares the palms and soles (p 162)

Pseudomonas Bacteremia 'Echthyma gangraenosum' is characterized by macules or vesicles (particularly in the axillae, abdomen, thighs, and anogenital region) that become pustular or necrotic (p 165)

Actinomycosis Sinus formation and sulfur colored granules (not specific) may be the first clues to this infection (Figure 83 and p 168)

Trichinosis 'Splinter' hemorrhages of the nails and conjunctival petechiae are characteristically noted with this infestation (Figures 32 and 87) (p 173)

Leprosy A diffuse granulomatous infiltration with pigmented and depigmented macules, papules, and also nodules is observed in the commoner lepromatous type anesthesia may develop either with skin lesions or independently in apparently normal areas anhidrosis is another early feature, infiltrative, ulcerative and scarring granulomas of the skin and mucous membranes occur in the tuberculoid form of the disease (p 176)

When confronted with an unexplained chronic dermatitis characterized by a dermal lymphocytic infiltrate, pathologists should process the biopsied specimens with satisfactory acid fast stains and examine the small dermal nerves for possible leprosy [636] This is especially important in the Southwest (because of the large Mexican population there) and along the Gulf coast if this infectious disease is to be recognized and treated early

Yaws The primary lesion or 'mother yaw' usually appears as a chronic granulomatous or ulcerative lesion on the exposed parts of the feet or legs satellite papules a secondary exanthem, areas of mottled pigmentation and depigmentation of the hands and feet, juxta articular nodules (Figure 22), and destructive tertiary lesions of an ulceroserpiginous nature

resemble the pattern of syphilis This infection is particularly common in the West Indies and in South America

Anthrax Several days after the inoculation, an inflammatory papule appears It progresses rapidly as a bullous lesion that contains either blood or pus, and is characteristically surrounded by a ring of vesicles and an intense inflammation The subsequent development of a shallow ulcer with a black eschar and even gangrene is almost pathognomonic The potential serious systemic consequences of cutaneous anthrax must be borne in mind Fortunately, the lesions are curable or preventable by the use of penicillin

The majority of these infections have resulted from contact with infected animals (particularly among farmers, butchers and veterinarians), or from the handling of infected hides skin, wool, or animal furs and hair as in tanneries wool scouring and carpet manufacturing[1412] (About 90 per cent of the cases of industrial anthrax can be traced to the infected goat hair that is imported from the Near East and which is woven into interlining material) While there are no authentic instances of this infection in humans caused by the drinking of contaminated milk or the ingestion of contaminated meat, there have recently been a number of severe outbreaks among cattle in several states which have necessitated a quarantine on the sale of milk and livestock The considerable resistance of the *Bacillus anthracis* organism (the spores of which can remain viable in the soil for as long as twenty five years) introduces the potential danger that these spores may be brought to the surface when land is flooded or eroded by heavy rains

Rat bite Fever An extensive morbilliform or macular eruption develops, particularly over the extensor surfaces and becomes confluent as reddish or purplish plaques (p 176)

Coccidioidomycosis Skin nodules appear that are painless, deep-seated, and pink to dusky red, they may ulcerate, exuding a grayish yellow pus, fungating papillomatous granulomas erythema nodosum and lesions resembling sarcoid and lupus vulgaris also have been noted (Figures 14 and 84, and p 166)

Sporotrichosis The localized lymphangitic form of this disease usually assumes a rather typical appearance with the development of a series of subcutaneous nodules several weeks after some minor trauma to the skin (particularly a scratch with a thorn or a sliver) It may be confused with actinomycosis, other granulomatous processes, and even carcinoma Hematogenous dissemination should be suspected when multiple nodules are found over many areas of the body The relative specificity of iodide therapy and the serious sequelae of systemic spread enhance the importance of prompt recognition of this disorder (p 170)[613]

Histoplasmosis Persistent ulcerative granulomas tend to develop in the mucocutaneous areas and mucous membranes in the progressive form of Darling's disease (Figure 86) Other less frequent dermal changes include papular eruptions, purpura, sarcoid like tumors, and chronic abscesses (p 167)

Infectious Mononucleosis A transient nonpruritic maculopapular or roseolar exanthem may appear about the fifth day, especially over the

trunk and lower limbs it has recurred with exacerbations of the condition Other dermadromes include urticaria, purpura, and a morbilliform eruption Although all these rashes are infrequent, they should be borne in mind in view of the confusion that could arise if the patient also exhibits a biologic false-positive serologic reaction (p 198)

Lymphogranuloma Venereum The inguinal buboes and draining sinuses, along with the anorectal manifestations, are typical Other dermadromes that may accompany the constitutional features of this disease include erythema nodosum, erythema multiforme, and ulcerations (p 155)

Malaria In addition to the pallor and hyperpigmentation in active untreated malaria there may be herpes simplex (rather common), herpes zoster, chloasma like pigmentation of the face and mucous membranes, various exanthems and serious Vincent's infection of the skin and mucous membranes

Bubonic Plague An itchy maculopapule at the site of the inoculation is transformed into a vesicle and then a lesion resembling a carbuncle A localized or generalized adenitis, and extensive petechiae or ecchymoses with a predilection for the extremities neck, and breasts may subsequently take place

The *differential diagnoses of a primary skin lesion and an associated indolent regional lymphadenitis*, with or without suppuration and beadlike subcutaneous nodules, should include the following entities

Cat-scratch disease	Cutaneous leishmaniasis
Tularemia	Lymphatic tuberculosis
Lymphogranuloma venereum	Bacterial adenitis
Sporotrichosis	Rickettsialpox
Blastomycosis	Anthrax
Glanders	Syphilis

Erythema nodosum (Figure 5) may be a manifestation of coccidioido mycosis, tuberculosis, lymphogranuloma venereum, streptococcosis, and trichophytosis (p 313)

In an analysis of a *chronic nonmalignant ulcer*, the differential diagnosis should include not only syphilis and tuberculosis but also diphtheria (Figure 88), amebiasis cutis, actinomycosis, yaws coccidioidomycosis, blastomycosis, and rat bite fever

Miscellaneous Dermadromes

Gastrointestinal Disorders

Aside from the melanin spots (Figure 2) in intestinal polyposis and the occurrence of acanthosis nigricans (Figure 1) in gastrointestinal malig nancy, only a few characteristic dermadromes of gastrointestinal disease are commonly encountered These include the following *Hypochlorhydria*—rosacea, *chronic pancreatitis*—xanthomatous (Figures 10 and 11) infiltra tions (p 48) *acute hemorrhagic pancreatitis*—the Gray Turner sign (local ized areas of bluish discoloration about the umbilicus and the loin from the extravasation of the hemorrhagic peritoneal fluid) and Walzel s sign (a reticulated brownish gray discoloration of the abdomen and chest resem bling livedo reticularis) (Figure 96) [1411] *ulcerative colitis*—hyperpigmenta

tion of the body, erythema nodosum, temporary redness of the hair,[1316] erythema multiforme, urticaria, aphthous stomatitis, condyloma acuminata, and chronic, indolent, pyogenic ulcers, especially of the legs (p 50) *intestinal lipodystrophy* (Whipple's disease)—increased body pigmentation, usually in association with arthritis in males (p 47), *intestinal parasites*—urticaria, eczema, and pruritus ani, *sprue*—lesions occur similar to those associated with avitaminosis B (p 46), *metastatic functioning carcinoid tumors of the small bowel*—transient vasomotor phenomena and telangiectases, especially over the face and neck (Figure 7) (p 347) A number of these and other disorders that involve both the gastrointestinal and cutaneous systems were recently reviewed by Beerman and Greenbaum [1414]

Respiratory Disorders

Cyanosis and clubbed fingers (Figure 34) are frequently associated with chronic respiratory diseases Acrocyanosis, cyanosis of the distal nail beds, half moons absent from the finger nails, acne, malar flush, red palms, and telangiectasia (Figure 41) of the thorax may be suggestive of *pulmonary tuberculosis* *Pneumonia* is sometimes accompanied by cyanosis of the lips and nails, small bullae, and herpes simplex *Bronchial asthma* of allergic origin is often associated with a neurodermatitis *Lung cancer* can be heralded by a pachydermoperiostitis (Also see Group XI, p 325)

Rheumatic Diseases

The common dermadromes of *rheumatoid arthritis* are hyperhidrosis, red palms, and persistent firm, tender subcutaneous nodules near the joints (Figure 21) Arthritis (especially involving the small joints of the hands and feet) and psoriasis occur together often enough to merit the designation of *psoriatic arthritis*

The dermadromes of *rheumatic fever* are legion They include urticaria, petechiae, purpura (Figure 6), excessive sweating, erythema nodosum (Figure 5) and erythema multiforme (Figure 8) Another is erythema marginatum (Figure 9), with its bizarre patches on the torso and upper portions of the arms and legs and red swollen patches over the joints Persistent, enlarging, nontender, juxta articular nodules (Figure 22) are frequent, as are the dusky red, movable, nontender deep nodules about the head and hands (Figure 21) (Also see Group X, p 310)

Cardiovascular Disorders

Cyanosis and ankle edema are among the cardinal signs of heart disease Varying degrees of *jaundice* can be present in tricuspid stenosis, constrictive pericarditis, and in advanced right sided failure—with or without pulmonary embolism and infarction

It is necessary for at least 25 per cent of the circulating blood to be shunted in order to create recognizable *cyanosis* The cyanosis of congenital heart disease that makes its initial appearance somewhat later in life is often due to either an auricular septal defect or the Eisenmenger complex

In transposition of the great vessels the cyanosis is more intense over the head and extremities, whereas only the lower extremities appear cyanotic in the patient with a patent ductus arteriosus in which there is a reversal of the blood flow (p 286)

Clubbing (Figure 34) in congenital heart disease usually bears a direct relationship to both the degree and distribution (but not necessarily the duration) of the cyanosis, and to the polycythemia When cyanosis is absent one must entertain the possibility of a complicating pulmonary disorder or a bacterial endocarditis

Other significant associations include the following

Mitral Stenosis The malar flush, yellow forehead, blue lips, and cold cyanotic hands are classic

Coronary Disease Pitting and transverse furrowing of the nails often date an acute occlusive episode Xanthoma tuberosum (Figure 10) and xanthelasma frequently accompany atherosclerosis with or without coronary disease (Also see Group IX, p 266)

The Superior Vena Caval Syndrome The various causes resulting in the characteristic *cyanosis, edema and venous distention of the face neck,* and upper extremities (Figure 45) have been enumerated in Group XI (p 325)

Dissecting Aneurysm of the Aorta The presence of ecchymoses on the chest abdomen or lumbar regions should be sought out when a dissecting aneurysm and retroperitoneal hemorrhage are suspected (p 295) This is similar to the Cullen s sign noted with intraperitoneal hemorrhage

Endocarditis Pinkish petechiae and purpuric spots of the skin and conjunctivae appear either singly or in showers They are commonly found on the inside of the palms and on the soles of the feet Other features include the following clubbing (Figure 34) splinter hemorrhages' (Figure 32) tender, sometimes bleeding, and pigmented spots on the fingers and toes the painless Janeway lesion consisting of a small erythematous patch on the palms and soles, and Osler s nodes The latter are small red tender nodules on the fingertips foot pads and the thenar or hypothenar eminences The combination of lupus erythematous like lesions and a verrucous endocarditis characterizes the *Libman Sacks disease* It is pointed out that there have been instances in which petechiae, "splinter hemorrhages" under the nails and other evidences of embolism occurred in patients with rheumatic carditis in whom no endocarditis could be demonstrated (p 115)

An accessory nipple is an anomaly that is very frequently associated with *congenital heart disease* The same applies to hemangiomas, spina bifida, harelip polydactyly, syndactyly and mongolism

Arachnodactyly (Figure 90) should direct attention to Marfan s syndrome with its high incidence of septal defects, vascular hypoplasia and medionecrosis of the aorta (p 425) [1254 1 56]

Peripheral Vascular Disorders

Pallor on elevation rubor on dependency cutaneous atrophy ulcerations, varicosities nail changes sweat disturbances pigmentation and sec-

ondary infection are frequent manifestations of significant peripheral vascular disease. Erythromelalgia and the Raynaud syndrome can occur as "primary" disorders, or they may be secondary to a host of systemic diseases. Among the latter are diabetes mellitus, arteriosclerosis obliterans, Buerger's disease, hypertension, the dyscollagenoses, leukemia, cryoglobulinemia, and thrombohemolytic thrombocytopenic purpura (p. 219).[803] The unexplained presence of recent thrombophlebitis (Figure 42) or Raynaud's phenomenon should alert the clinician to the possibility of an underlying malignancy.[786, 787]

Sarcoidosis

Small sarcoma-like cutaneous tumors in groups or in infiltrated plaques, with borders of bright red, bluish red, or brownish yellow, usually occur on the arms, shoulders, and face (Figure 27). They rarely ulcerate, although atrophic scars often mark the sites of previous lesions. Lupus pernio describes the diffuse infiltration and thickening of the skin affecting the face, eyelids, nose, and ears. The lacrimal and parotid glands are frequently enlarged. Firm sarcoid nodules are occasionally found at the interphalangeal joints. In contrast to tuberculosis, it is most unusual for sarcoidosis to produce draining sinuses (p. 205).[742, 744] The possibility that sarcoidosis may be present without any cutaneous involvement must be frequently entertained.

Fat Embolism

Within the first three days of the traumatic episode, a dark red petechial eruption may appear over the chest, shoulders, neck, and the upper extremities (p. 216).[792]

Polyostotic Fibrous Dysplasia (Albright's Syndrome, Osteitis Fibrosa Disseminata)

The classic form of polyostotic fibrous dysplasia (wherein striking changes occur in the skin and in other systems of the body) may first be recognized. More often, however, the diagnosis is arrived at only after much effort in evaluating asymptomatic bone lesions of "formes frustes."

In the "complete" or classic form, one encounters the triad of (1) a self-limited disseminated osteitis fibrosa of both the hyperostotic and hypoostotic types with the characteristic segmental distribution and "torn paper" appearance, (2) areas of very irregular brown pigmentation which are also seen on either side of the midline particularly on the buttocks, sacrum, and upper spine, and (3) a true sexual and somatic precociousness in females, probably due to hypothalamic irritation (Figure 64). The café au lait pigmentation (which can also involve the mucous membranes) contains excessive melanin and therefore may appear very similar to that seen in Addison's disease and neurofibromatosis. Other associated phenomena include hyperthyroidism, diabetes mellitus, congenital arteriovenous aneurysms, rudimentary kidneys, atrophy of the optic nerve, and mental deficiency (p. 413).[1, 16]

The Germinal Dysplasias

The *congenital ectodermal defect* (Figure 91) may be characterized by hypotrichosis, absence of the sweat and sebaceous glands, adontia or hypodontia, absence or malformation of the nails, a characteristic facies (viz, thick lips, sunken cheeks, a pointed chin, and a "saddle" nose), and even the absence of mammary glands[1229] None of these patients demonstrate cataracts, and the skin is usually smooth and fine

In the *multiple germ plasm dysplasias*, one finds numerous classical and 'formes frustes variations in the separate entities For example, *Werner s syndrome* is characterized by shortness of stature premature graying of the hair, premature baldness, scleropoikiloderma trophic ulcers at the pressure points over the heels toes and ankles (due to the tight skin and associated poor subcutaneous fat tissues), hyperkeratosis of the feet juvenile cataracts with starlike opacities, hypogonadism diabetes mellitus calcification of blood vessels osteoporosis, and metastatic calcifications[1 7]

In *Rothmund's syndrome*, the cataracts and telangiectasia appear earlier in life (between three months to six years) The skin is generally thin and pliable with no ulcerations[1227]

In *progeria with nanism* (Figure 94)(Hutchinson Guilford) the children are dwarfed, sexually retarded, and have a taut or wrinkled atrophic skin with little hair[1230] They exhibit premature senile changes and usually die before the third decade No familial tendency, pressure ulcers, or cataracts characterize this entity

Angiokeratoma Corporis Diffusum Universale (Fabry)

This very unusual systemic condition can be readily confused with the various purpuras hereditary telangiectasia and certain skin disorders The term angiokeratoma refers to the small raised and partially hyperkeratotic vascular aneurysms that are present on the skin The lesions are initially restricted to the lower part of the trunk or to the upper part of the lower extremities with a centripetal distribution in groups (Figure 43) Various organs are also affected by these aneurysms, including the retinae, joints, myocardium lungs and the gastrointestinal tract[8 1]

Calcinosis Cutis

Three forms of such calcification are described In re likely that the terms calcinosis circumscripta and ca merely describe two varieties of the same process of interst This metabolic disorder (Figure 50) is characterized by the calcium phosphate in the skin and in the subcutaneous tissu ments tendons nerve sheaths and fascias) The fact that cations occur only infrequently in interstitial calcino is is of tance in differential diagnosis Normal concentrations of bo inorganic phosphorus are almost always found in the se wise no alteration in the normal response to calcium

ondary infection are frequent manifestations of significant peripheral vascular disease Erythromelalgia and the Raynaud syndrome can occur as "primary" disorders, or they may be secondary to a host of systemic diseases Among the latter are diabetes mellitus, arteriosclerosis obliterans, Buerger's disease, hypertension, the dyscollagenoses, leukemia, cryoglobulinemia, and thrombohemolytic thrombocytopenic purpura (p 219)[803] The unexplained presence of recent thrombophlebitis (Figure 42) or Raynaud's phenomenon should alert the clinician to the possibility of an underlying malignancy[786, 787]

Sarcoidosis

Small sarcoma-like cutaneous tumors in groups or in infiltrated plaques, with borders of bright red bluish red, or brownish-yellow, usually occur on the arms, shoulders, and face (Figure 27) They rarely ulcerate although atrophic scars often mark the sites of previous lesions Lupus pernio describes the diffuse infiltration and thickening of the skin affecting the face, eyelids nose, and ears The lacrimal and parotid glands are frequently enlarged Firm sarcoid nodules are occasionally found at the interphalangeal joints In contrast to tuberculosis, it is most unusual for sarcoidosis to produce draining sinuses (p 205)[74-744] The possibility that sarcoidosis may be present without any cutaneous involvement must be frequently entertained

Fat Embolism

Within the first three days of the traumatic episode a dark red petechial eruption may appear over the chest shoulders, neck, and the upper extremities (p 216)[792]

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is paper thin, the subcutaneous fat becomes considerably reduced, and the subcutaneous vessels appear quite prominent While scleroderma might subsequently occur in a number of these individuals, scleroderma, involvement of the finger tips and sclerodactylia *per se* are not characteristic of acrodermatitis chronica atrophicans Other features include calcification of the soft tissues, the formation of nodules hypergammaglobulinemia, and atrophy of the adjacent bones Poikiloderma might also be a counterpart of scleroderma, in which case the designation of scleropoikiloderma is used

Poikiloderma Vasculare Atrophicans (Jacobi)

This uncommon disorder occurs in adults and may closely simulate a radiodermatitis because of the associated atrophy telangiectasia and patchy mottled pigmentation (Figure 92) It is significant because of the frequency with which it might subsequently be found to be associated with dermatomyositis (poikilodermatomyositis) scleroderma (scleropoikiloderma), or one of the leukemias or lymphomas

believed that interstitial calcinosis may arise from an abnormal affinity of the mucopolysaccharide of ground substance for calcium [1410]

Calcinosis Cutis Circumscripta In this localized form, the lesion occurs at sites that are subjected to considerable trauma (i e, along the flexor tendons of the hands and the extensor tendons of the elbows and knees) As the subcutaneous nodules or tumors enlarge, the overlying skin becomes involved and ultimately ulcerates, discharging a creamy material with calcium particles "Chalk gout" is most frequently encountered in menopausal women and may be associated with Raynaud s disease, scleroderma, and acrodermatitis chronica atrophicans

Calcinosis Universalis Calcinosis universalis affects the deeper subcutaneous tissues and the dermis, particularly over the proximal extremities and the pelvic girdle A septic syndrome with huge cold abscesses may ensue Scleroderma, Raynaud's disease, dermatomyositis, and sclerodactylia are often also present

Metastatic Calcinosis Metastatic calcinosis is associated with many of the hypercalcemic states (hypervitaminosis D, extensive bone destruction, the milk alkali syndrome), myelogenous and lymphatic leukemia, and the Cushing syndrome It is of interest that not only is extensive subcutaneous calcification actually unusual in hyperparathyroidism, but that it is more prone to occur in hypoparathyroidism

Progressive Lipodystrophy

This condition chiefly affects children following certain acute infectious diseases particularly encephalitis There is a progressive, diffuse, and symmetrical loss of subcutaneous fat, producing an emaciated appearance over the upper half of the body

Chronic Radiodermatitis

Chronic radiodermatitis is characterized by a dry, pruritic, and atrophic skin Other features include diffuse pigmentation, freckle-like spots nail changes, suppurative paronychia, telangiectases small keratoses, and at times malignant degeneration

The Sjogren-Mikulicz Syndrome

In addition to the keratoconjunctivitis sicca the patient often exhibits a dry skin, Raynaud s phenomenon telangiectases, alopecia, scleroderma like changes, xerostomia, and rhinitis sicca (p 414) Two other components of this entity include a chronic polyarthritis and enlargement of the parotid or other salivary glands (Figure 95) [1219, 1220]

Acrodermatitis Chronica Atrophicans

This condition consists of an unusual diffuse atrophy of the skin that affects the limbs, most commonly in middle-aged females After the initial edematous and erythematous phase, the atrophic phase sets in The skin

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PART TWO

A Classification and Analysis of Useful Diagnostic Procedures



INTRODUCTION

> The erratic course that our profession has followed its blind alleys and pitfalls the methods of thought observation and experience that have proved profitable or fallacious in the past—comprehension of these should aid many of us today in recognizing the broader problems of the moment and in devising methods for their solution *

> Give him good methods and a proper point of view and all other things will be added as his experience grows —OSLER

THE ATTENDING physician or consultant who faces a difficult diagnostic problem may occasionally orient his approach more accurately by *reviewing additional methods of clinical investigation which might clarify* the issue Accordingly, this reference listing and analysis of useful diagnostic procedures is presented as both a summary and supplement to the contents of the preceding text and as a working guide for clinicians who will undoubtedly wish to modify the listing or to add additional entries

An apparent paradox has been repeatedly observed by numerous investigators working on diverse problems related to clinical medicine This pertains to the fact that the more one understands the indications for and the results of various diagnostic tests the less frequently they appear to be needed This consideration—along with the necessity of setting forth in a concise and analytic fashion the panorama of laboratory diagnosis for busy clinicians to review—justifies such a presentation in a book dealing with modern practical" diagnostics

On the other hand, the contemporary clinician must constantly make every effort to preserve his clinical acumen and judgment He must be guided by the natural history and prognosis of disease whenever he engages in the use of newer diagnostic and therapeutic techniques Mackenzie has aptly noted that When we search for the recondite and the obscure we fail to recognize the simple and the obvious

The author is not at all unmindful in this elaboration of biochemical physiological, and clinical techniques of the unfortunate decline in both the *enthusiasm for and the caliber of autopsy performance in the postgraduate* training of physicians This shift in emphasis has been most acutely experienced by clinicians engaged in the private practice of medicine particularly when they are removed from the larger municipal or state clinics and centers He is also aware of the frequency with which patients are subjected to a 'battery' of tests that results only in the exhaustion of the patient and the laboratory technician and more often than not produces merely

* Krumbhaar E B Editor's preface to *A History of Medicine* Arturo Castiglioni M D New York Alfred A Knopf 1947

an untidy array of unrelated facts Certainly, clinical judgment combined with the intelligent appraisal and interpretation of the many simple, inexpensive tests which are at the disposal of practically every physician are far more important to the welfare of most patients than the contributions of electronmicroscopy, vectorcardiography, and complicated chemical analyses All these approaches should be regarded as mutually complementary in the enhancement of clinical acumen, so that "footside medicine" will hold its proper relationship to "bedside medicine"

In a résumé of his interviews with patients who had been subjected to several routine diagnostic procedures within the previous day or two, Kaplan clearly presented ample evidence for his theme, "Laboratory Procedures as an Emotional Stress"[6] All physicians would profit from an awareness of the frequency with which severe psychological reactions occur in either uninformed or misinformed patients who are so examined Not only is fear generated by the apparatus itself, but unwarranted inferences are frequently drawn concerning the nature and gravity of the underlying illness Lumbar punctures, tuberculin testing, repeat chest films for minor abnormalities noted during mass surveys, electroencephalograms, and electrocardiograms are particularly apt to frighten unstable patients

The groupings to follow are self explanatory Although some tests might have been properly placed under other headings—for example, in the case of the endocrine function studies where pluriglandular syndromes are involved—the reasons for the present arrangement are usually quite apparent An attempt has been made to emphasize primarily those studies which are available to most physicians or which can be readily performed by radiologists and interested investigators in laboratories Several newer procedures which have already proved to be of considerable clinical promise, such as the serum transaminase, hemoglobin electrophoresis, and radioisotope uptake determinations with I^{131} and $Co^{60}B_{12}$, are also included In addition, the ever increasing role of histologic and pathophysiologic examination of tissue in the early diagnosis of many neoplastic and non neoplastic disorders will be stressed Such procedures are set forth not only in Sections X and XI (which are devoted to the direct biopsy procedures and exfoliative cytology), but also in Section II in the form of the many new serum enzymatic tests ("indirect tissue biopsy")

There will be occasional deviations from the general format in certain sections This is most notable in those dealing with "Cardiovascular Pulmonary Function" and with pancreatic function tests wherein certain studies that are usually performed only by expert clinical physiologists are listed Such an enumeration, however, serves as a convenient supplemental reference for the normal values and their significant variations

Following each test, a few pertinent remarks are presented relating to important technical factors that may influence the accuracy or interpretation of the result, and to inferences of particular interest to clinicians These comments must obviously be abbreviated and sketchy Nevertheless, they are considered by experienced consultants to represent the more important phases of that particular procedure

The combined importance of accurate and reliable techniques, the repetition of equivocal or inappropriate results, a continual degree of

healthy skepticism for laboratory reports and the ancillary supplementary role with which these tests should be regarded in the evaluation of difficult clinical problems cannot be overemphasized. For example, a number of authors have been impressed by the high degree of error from many laboratories in reporting results of the blood glucose and other common biochemical analyses when performed on submitted test specimens.[1-3]

Detailed discussions and charts pertaining to the significance of alkalosis, acidosis, the metabolic derangements in bone disorders, and the like have been intentionally omitted since it is felt they would defeat the purposes and brevity of this outline. In their place, I have substituted the somewhat unique presentation of three categories of studies posing great clinical interest—namely, "The Therapeutic Diagnostic Tests" (Section XIV), "The Withdrawal Tests" (Section XV), and "The Provocative Tests" (Section XVI).

Many texts, papers, manuals and charts have been consulted for clinical and technical assistance. Rather than emphasizing or limiting the references to reports in the various laboratory journals, the author has attempted to set forth in the bibliography to Part II the most comprehensive key reference papers he has personally encountered in the recent clinical literature. The interested reader will find them most profitable in his own studies. *References are omitted when the subject matter is either* so sufficiently well known as to obviate such emphasis, or when ample description and comment can be readily found in the general reference papers or in the more recent texts. In a further effort to integrate Part II with Part I of this book, attention is frequently directed back to the bibliography of the preceding text by the letter "T" followed by the appropriate reference numbers. In many instances, the actual page numbers of the text on which particularly relevant material may be found are also included.

SECTION I

Hematologic Studies

PERIPHERAL BLOOD CYTOLOGY

Total Leukocytes

NORMAL RANGE—TECHNICAL NOTES 5000 to 10,000/cu mm The ear lobe provides a desirable site for the preparation of blood films when abnormal white cells are being sought, owing to the greater selective filtering capacity of the vascular bed there This is particularly true in endocarditis other infections, and the leukemias—especially when a leukopenia is present (T-405b)

CLINICAL CLUES Increased in leukemia, leukemoid responses,(23) infection, and hemorrhage If leukopenia and infection are present, suspect lupus erythematosus, hematogenous tuberculosis, preleukemic leukemia and overwhelming infection Leukopenia may be caused by numerous drugs virus infections, a preleukemic phase (T-661) hypersplenism,(T-733-737) bone marrow hypoplasia or replacement, or it may be a cyclic phenomenon (T-521, 1211) The white blood cell count can be elevated in a number of viral infections and must not be used as the sole basis for differentiating them from bacterial infections

MYELOCYTES OR BLAST FORMS

NORMAL RANGE 0

CLINICAL CLUES May be seen in the leukemias (particularly myelocytic) and leukemoid reactions due to a variety of infections and neoplasms (23) In an overstained blood film *lymphoblasts can closely resemble mature small lymphocytes*

JUVENILE NEUTROPHILS

NORMAL RANGE 3 to 5 per cent

CLINICAL CLUES A shift to the left commonly occurs in infections In the Pelger Huet anomaly, there is a familial false shift to the left due to arrested segmentation of the granulocytic nuclei at the 2 lobe level (The total white cell count is normal, however)(25)

SEGMENTED NEUTROPHILS

NORMAL RANGE 50 to 65 per cent

CLINICAL CLUES May be increased without a corresponding rise in the total white blood cell count in hematogenous tuberculosis and in leptospirosis *Characteristic* multi lobed nuclei are found in pernicious anemia

EOSINOPHILS

NORMAL RANGE 1 to 3 per cent (50 to 300/cu mm total eosinophil count)

CLINICAL CLUES Eosinophilia occurs in various malignancies (T-1020, 1021) skin diseases, parasitic diseases drug treatments, allergic states, and myelocytic leukemia If present during stress one should suspect adrenocortical insufficiency (130 144) (Also see Adrenal Cortex in Section V p 733)

BASOPHILS

NORMAL RANGE 0 to 1 per cent

CLINICAL CLUES Increased in chronic myelocytic leukemia myeloid metaplasia lymphoma polycythemia vera and other causes of bone marrow stimulation A transient relative basophilia may follow irradiation

LYMPHOCYTES

NORMAL RANGE 25 to 35 per cent

CLINICAL CLUES Increased in pertussis infectious lymphocytosis, lymphocytic leukemia, healing infections and granulocytopenia Atypical virocytes are seen in infectious mononucleosis (T-725) The large vacuolated virocytes (Downey cell, type II) have been mistaken for the unusual leukocytes that circulate in certain stages of subacute or chronic leukemia Lymphopenia and neutropenia with recurrent infections should suggest hypogammaglobulinemia (T-525 526) One of the characteristic features of rubella is the regular appearance of many plasma cells and Turk cells by the tenth day, which persist for many weeks (22)

MONOCYTES

NORMAL RANGE 3 to 7 per cent

CLINICAL CLUES Increased in certain infections (tuberculosis brucellosis the rickettsioses) monocytic leukemia and certain poisonings (tetrachlorethane) The diagnosis of a chronic monocytic leukemia is usually in error and commonly refers to the monocytic phase of a chronic myelogenous leukemia

CELLS WITH AUER BODIES (elongate structures in the cytoplasm of early *undifferentiated cells)*

NORMAL RANGE 0 (May be seen in normal histiocytes)

CLINICAL CLUES These bodies are presumptive evidence of leukemia, particularly the myelocytic or monocytic types

SMUDGE AND BASKET CELLS

NORMAL RANGE—TECHNICAL NOTES 0 (If present they often represent artifacts)

CLINICAL CLUES Smudge and basket cells are constant features in the peripheral blood of certain leukemic patients particularly in chronic lymphatic leukemia

L E CELLS (15 21) (T-925 940)

NORMAL RANGE—TECHNICAL NOTES Negative

Using the buffy coat of centrifuged defibrinated blood is a more sensitive method than using heparin or studying the marrow, but more false-positives are so noted The finding of L E cells is more diagnostic than rosettes (clusters of polymorphs about a hematoxylin body) Dubois has suggested that at least three different L E cell test methods be performed to screen a suspected case adequately (i e utilizing two concentrations of heparin as an anticoagulant clot maceration and the Snapper ring technique) (T-940)

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NUCLEATED R B C

NORMAL RANGE 0

CLINICAL CLUES Found in myeloid metaplasia (26) (T-738) thrombohemolytic thrombocytopenic purpura acute hemorrhage erythroleukemia acute hemolytic crises and extensive bone marrow invasion This is a poor prognostic sign (37)

SPHEROCYTES

NORMAL RANGE—TECHNICAL NOTES 0 (A thin blood smear is essential)

CLINICAL CLUES Found in congenital spherocytosis and in other types of hemolytic disease

TARGET CELLS

NORMAL RANGE 0

CLINICAL CLUES Present in the thalassemia and sickle cell syndromes particularly hemoglobin C disease (13) (T-716-722)

SICKLE CELLS

NORMAL RANGE—TECHNICAL NOTES 0 Various techniques are employed These include sealed preparations (which may be unreliable) displacement of oxygen with carbon dioxide, and the use of various reducing agents such as sodium metabisulfite (20)

CLINICAL CLUES Sicklemia is found in 7 to 10 per cent of American Negroes A test for sickle cells should be performed in any vague syndrome affecting the joints abdomen heart and central nervous system in this racial group (p 195) (T-711 714)

OVALOCYTES

NORMAL RANGE 0

CLINICAL CLUES Ovalocytosis or familial poikilocytosis is usually a benign disorder that is transmitted as a Mendelian dominant characteristic The regular elongated and sausage-shaped appearance with rounded ends distinguishes these cells from both ordinary poikilocytes and sickle cells Furthermore there is no increase in their number in an atmosphere of high carbon dioxide tension Evidence of increased blood destruction has been found in about 12 per cent of individuals with ovalocytosis (the term being used only when at least 10 per cent of the red cells show this feature)

HOWELL-JOLLY BODIES AND OTHER INTRAERYTHROCYTE INCLUSION BODIES

NORMAL RANGE 0

CLINICAL CLUES Splenic agenesis may be suspected by the finding of many Howell Jolly bodies in the circulating erythrocytes along with target cells decreased osmotic fragility siderocytosis and leukocytosis This is particularly true in the patient with congenital heart disease (p 426) (T-524 683)

Heinz bodies are another specific type of erythrocytic inclusion but require special staining Their presence is also highly suggestive of congenital asplenia provided toxic factors have been excluded (T-524) A Heinz body anemia may also be the basis of a hemolytic anemia in the newborn with jaundice (T-704c)

In addition to Howell Jolly and Heinz bodies other intraerythrocytic inclusion bodies may become more numerous after a splenectomy These include siderocytes (red blood cells with one or more granular inclusion bodies that contain sufficient ferric iron to give a positive Prussian blue reaction) red cell nuclei malarial plasmodia and the organisms of bartonellosis (12)

Polymorphonuclear nucleophagocytes with homogenized secondary nuclei are noted at times in hypersensitivity states This is in contrast to the lack of homogenization that has been seen occasionally in normal persons and in patients with miscellaneous diseases (21b)

CLINICAL CLUES *This test may* be positive only during exacerbations of lupus erythematosus It is negative in 30 per cent of typical cases of systemic lupus Positive tests occur infrequently in penicillin hypersensitivity, after certain chemotherapeutic agents (especially Apresoline and Dilantin), miliary tuberculosis, *pernicious anemia in relapse*, *dermatitis herpetiformis*, myeloma, during cortisone withdrawal, moniliasis and with chronic liver disease (39) (T-926, 927)

The transient presence of the L E cell phenomenon in hypersensitivity states contrasts with its persistence in patients with untreated classical lupus erythematosus *The L E phenomenon was found as a nonspecific response in 25 of 91 patients* who presented with the classic clinical picture of rheumatoid arthritis (T-926)

Platelets

NORMAL RANGE—TECHNICAL NOTES 250,000 to 400,000/cu mm (A special sequestrene tube should be used or blood should be drawn directly into an erythrocyte counting pipette which has been rinsed with 14 per cent magnesium sulfate solution *All glassware must be meticulously clean to give accurate results*)

CLINICAL CLUES Increased in chronic myelocytic leukemia myeloid metaplasia hemorrhage after splenectomy and polycythemia vera Diminished in the thrombocytopenic purpuras (primary and secondary) chemical poisoning the leukemias, Banti s disease, Gaucher s disease, and *after* repeated *transfusions Unusual* forms of platelets are also found in myelofibrosis (26) The levels of the circulating platelets in chronic myelogenous and chronic lymphocytic leukemia are often the determining factors in the selection of therapeutic agents (particularly P^{32})

MEGAKARYOCYTE FRAGMENTS

NORMAL RANGE 0

CLINICAL CLUES *Found in myelofibrosis (over half the cases in which* they are sought),(26) sepsis, Hodgkin s disease chronic granulocytic leukemia and polycythemia vera Their appearance might indicate a change in the character of the latter two diseases

Red Blood Cells

NORMAL RANGE Males—4 6 to 6 2 million/cu mm Females—4 2 to 5 4 *million/cu mm*

CLINICAL CLUES (See Groups VI and XI of Part I for the differential diagnosis of obscure anemias pp 189 and 324) If numerous rouleaux are noted suspect a myeloma It is important to differentiate between polycythemia vera and relative polycythemia due to a low plasma volume (T-681) An iatrogenic ' anemia in females may be avoided by noting their normally lower counts

RETICULOCYTES

NORMAL RANGE 0 to 2 per cent

CLINICAL CLUES Increased in hemolytic anemia and in pernicious anemia during treatment One should be suspicious as to the sole hemolytic nature of an anemia if the reticulocyte count is less than 7 per cent

PER CENT BASOPHILIC 0 3 (0 to 0 5)

CLINICAL CLUES Elevated in chronic myelocytic leukemia, pernicious anemia and polycythemia vera (Also see Peripheral Blood Cytology for the significance of eosinophilia and basophilia)

METAMYELOCYTES (JUVENILE FORMS)

PER CENT 22 (13 to 32)

CLINICAL CLUES Elevated in shifts to the left and in agranulocytosis

POLYMORPHONUCLEAR LEUKOCYTES

PER CENT NEUTROPHILS 20 (7 to 30)

PER CENT EOSINOPHILS 2 (0 5 to 4)

PER CENT BASOPHILS 0 2 (0 to 0 7)

CLINICAL CLUES Elevated in chronic myelocytic leukemia myeloma iron deficiency anemia, and purpura hemorrhagica (Also see Peripheral Blood Cytology) The eosinophil count may be of prognostic value in primary thrombocytopenic purpura Patients with a high eosinophil index (i e more than 5 eosinophils per 100 granulocytes at the metamyelocyte or maturer stages) exhibit a marked tendency for spontaneous recovery have a higher rate of cure by splenectomy or steroids and a have a low operative mortality The reverse is true when a low index is present (36)

LYMPHOCYTES

PER CENT 10 (3 to 17)

CLINICAL CLUES Elevated in chronic lymphocytic leukemia and myeloma

PLASMA CELLS

PER CENT 0 4 (0 to 2)

CLINICAL CLUES Plasmacytosis (more than 5 per cent) is most marked in myeloma A reactive plasmacytosis with mature plasma cells may be striking in amyloidosis (T–204) various chronic infections hypersensitivity states the collagen disorders cirrhosis and metastatic neoplasms (T–673) They are usually absent in hypogammaglobulinemia Steroid therapy may be more effective in myeloma that is characterized by a less differentiated type of plasma cell response

MONOCYTES

PER CENT 2 (0 5 to 5)

CLINICAL CLUES Increased in monocytic leukemia(T–514 515) and macroglobulinemia

RETICULUM CELLS

PER CENT 0 2 (0 1 to 2)

CLINICAL CLUES Increased in the leukemias pernicious anemia and the hemolytic anemias These premature stem cells can only be identified as specific blast forms when accompanied by larger numbers of their differentiated cells

MITOTIC FIGURES

PER CENT 0

CLINICAL CLUES May be seen in the leukemias pernicious anemia and the hemolytic anemias

RUSSELL BODIES (acidophilic cytoplasmic inclusions)

PER CENT 0

CLINICAL CLUES These bodies consist of mucoprotein and are usually

BONE MARROW CYTOLOGY

Marrow can be satisfactorily aspirated from the sternum, the anterior or posterior iliac crests (less anxiety is incurred using these sites, but there is more likelihood of dilution with peripheral blood), and the spinous processes of the lumbar vertebrae (particularly when multiple punctures are to be performed) For infants and children under the age of 4, a point on the tibia about 3 cm below the knee cap may be preferred (33, 34) The importance of procuring small amounts of undiluted marrow for cytologic study is stressed Repeated "dry taps" may be highly significant (i e, fibrosis metastases, lymphoma, and infection) (T-690) If marrow is not obtained at the first attempt, aspiration with considerable suction should be repeated at several sites Should these maneuvers still prove to be unsuccessful a bone marrow biopsy is usually in order

There are various methods of processing the remaining aspirated material after the slides have been made from the concentrated marrow These include (1) the performance of a hematocrit on the marrow blood which is placed into a heparinized paraffin lined vial (for the myeloid-erythroid ratio), (2) paraffin sections on the remainder of the aspirate after its immersion into alcohol, (3) processing of the collected bone marrow particles in paraffin sections after immersion into acidified Zenker s fluid, and (4) the application of an iron stain (*vide infra*) for an indication of the level of the iron stores in the body (38) Cultures can also be made (See Section VI)

Biopsy of the bone marrow with the Vim-Silverman needle has been shown to be as rewarding as formal surgical trephines in those instances wherein dry taps are encountered, notwithstanding repeated aspirations and the use of the selective particle technique (24) The needle with obturator is inserted approximately 1 cm cephalad to the posterior superior spine of the ilium on the posterior iliac crest Once inside the cortex of the bone, the biopsy blades are introduced the remainder of their length, and both the cannula and biopsy blades are removed as one unit The marrow plug is then isolated, placed in Zenker s solution for fixation (24 hours usually will suffice for sufficient decalcification) and then subjected to routine histological and staining processing Not only does this procedure obviate the presence of bone ' dust and the anxiety attendant upon surgical biopsy, but one is able to preserve for study the normal relationship of the marrow and bone trabeculae without the presence of cortex

At least 300 cells must be counted for an accurate differential count of bone marrow

Granulopoietic Series

MYELOBLASTS

PER CENT 2 (0 3 to 5)

CLINICAL CLUES Elevated in acute leukemia, chronic myelocytic leukemia, lymphoma and agranulocytosis

PROMYELOCYTES

PER CENT 5 (1 to 8)

CLINICAL CLUES Elevated in chronic myelocytic leukemia and leukemoid reactions

MYELOCYTES

PER CENT NEUTROPHILIC 12 (5 to 20)

PER CENT EOSINOPHILIC 1 5 (0 5 to 3)

malignant spread is the fact that such metastatic invasion usually takes place not in the form of sheets of cancerous cells, but as individual malignant cells whose morphology closely resembles that of reticulum cells and myeloblasts

Other Specific Cells

PER CENT 0

CLINICAL CLUES The typical Niemann Pick cell in the marrow is round or oval and is filled with many small hyaline droplets that impart a foamlike appearance to it The wavy fibrils in the cytoplasm of the large pale and polyhedral Gaucher cells give these cells a wrinkled appearance that is diagnostic (T–287)

Granulomas

PER CENT 0

CLINICAL CLUES Pease has noted granulomatous lesions in paraffin sections made from particles of bone marrow removed by aspiration from patients with tuberculosis, histoplasmosis brucellosis sarcoidosis infectious mononucleosis malignant lymphomas and a variety of other disorders (29) With the exception of the first three diseases mentioned in which the causal organisms might be identified no distinctive histopathologic characteristics can usually be delineated

Iron Granules

PER CENT Smeared-out fragments of bone marrow are examined for iron granules either directly (in the form of golden yellow granules) or by staining the aspirate or sections Yellowish brown granules in hematoxylin-eosin azure sections may introduce misleading artifacts The fixation of either stained or unstained slides by formalin vapor in a Coplin jar facilitates the subsequent staining of the marrow with Prussian blue (38b)

CLINICAL CLUES The evaluation of sternal marrow for stainable iron has been shown to be more reliable than the determination of the serum iron and iron binding capacity in the diagnosis of iron deficiency The bone marrow iron stain also affords a ready method of differentiating the hypochromic anemia of iron deficiency from the hypochromic anemia of thalassemia (T–722) Similarly whereas normal bone marrow contains from 24 to 81 per cent sideroblasts iron granules are usually absent in the normoblasts of patients with marked iron deficiency (14) Increased iron stores have been observed in pernicious anemia uremia cirrhosis disseminated lupus erythematosus hemosiderosis and hemochromatosis

SPLENIC BIOPSY

(See Section XI p 800)

STUDIES OF BLOOD CLOTTING AND DESTRUCTION (10)

Bleeding Time

NORMAL RANGE—TECHNICAL NOTES 3 to 5 minutes using a standardized incision on the forearm or lobe of the ear (the Jacobson method) (T–818d)

CLINICAL CLUES Prolonged in thrombocytopenic purpura hereditary hemorrhagic diathesis (pseudohemophilia) and other hemorrhagic disorders if the deficiencies are severe Several determinations at different sites may be necessary due to variations in the local vascular defects of the constitutional capillaropathies (T–818)

considered to be pathologic secretions found in parent plasma cells They have been noted not only in myeloma, but also in primary amyloidosis, malignant lymphomas with acquired hemolytic anemia, and cryoglobulinemia (27) In addition to the Russell bodies clear globules (referred to as Mott bodies) may be found to occupy the cytoplasm of the myeloma cells

Erythropoietic Series

PRONORMOBLASTS

PER CENT 4 (1 to 8)

CLINICAL CLUES Increased in the iron deficiency and the hemolytic anemias

NORMOBLASTS

PER CENT 18 (7 to 32)

CLINICAL CLUES Decreased in the leukemias and pernicious anemia Increased in the hemolytic iron deficiency and blood loss anemias, polycythemia, and purpura hemorrhagica

MEGALOBLASTS

PER CENT 0

CLINICAL CLUES Present in pernicious anemia sprue after total gastrectomy or intestinal anastomoses and Cooley s anemia (T-153 701 703) Following transfusion in pernicious anemia, the megaloblasts can disappear without a rise in the reticulocytes (T-693) A leukemoid reaction may obscure the megaloblastosis in pernicious anemia if infection produces a myeloid hyperplasia (T-692 694) Macrocytosis with a megaloblastic marrow also occurs on occasion in liver disease (T-700) and in panhypopituitarism (T-109)

Megakaryocytes

PER CENT 0 4 (0 03 to 3) (If necessary these cells may be differentiated from Reed Sternberg cells—which have been identified only very rarely in the marrow—by the periodic acid Schiff stain Only the cytoplasm of the megakaryocytes will take up this dye)(17)

CLINICAL CLUES Decreased (along with very few budding platelets) in purpura hemorrhagica Increased in polycythemia vera myeloid metaplasia Hodgkin s disease sepsis, and certain malignancies

M E Ratio

PER CENT 4 1 (3 to 5 1)

CLINICAL CLUES The ratios may vary from 40 1 in chronic myelocytic leukemia to 1 1 in the hemolytic anemias

Tumor Cells

PER CENT 0

CLINICAL CLUES The routine search for tumor cells in the presence of a cryptic anemia or fever may prove very rewarding (T-689) Correct technique is particularly important to such a study Some investigators question the reliability of identifying metastatic cells in films stained by the Wright s method, however (28) One of the difficulties in interpreting bone marrow specimens for possible

Capillary Fragility Test

NORMAL RANGE—TECHNICAL NOTES 10 to 15 petechiae/sq in on the fore arm (5 cm below the elbow after 10 minutes of cuff pressure on the arm at 90 mm Hg) provided the systolic pressure is not less than this

CLINICAL CLUES Positive in the nonthrombocytopenic purpuras (primary and secondary), scurvy scarlet fever and uremia

Erythrocyte Fragility Tests

NORMAL RANGE—TECHNICAL NOTES Slight hemolysis in 0 45–0 39 per cent NaCl Marked hemolysis in 0 42–0 36 per cent NaCl Complete hemolysis in 0 33–0 30 per cent NaCl (But osmotic changes *per se* do not occur in the blood) This test is actually of little value except as an adjunct to other diagnostic procedures

CLINICAL CLUES Increased (if hemolysis occurs in over 0 5 per cent NaCl) in congenital hemolytic anemia (16) Decreased (if hemolysis is incomplete in 0 3 per cent NaCl) in thalassemia sicklemia, and hypochromic anemia

Fibrinolysis (also see Fibrinogen, p 686)

NORMAL RANGE—TECHNICAL NOTES The stability of a clot of whole blood or recalcified plasma is observed at ½ 1 2 3 4 and 24 hours One must watch closely for coagulation since great fibrinolysis may give the erroneous impression of incoagulability of the blood

CLINICAL CLUES Partial or complete lysis of the clot occurs in fibrinogenolysis *Fibrinolytic purpura results from activation of the enzyme, plasmin on* the proteolytic enzymes It can occur during operations upon the prostate, lung and pancreas or in malignancy of these organs in shock burns transfusions and anaphylactoid reactions acute leukemia and severe liver disease (T–1291) There is usually an associated reduction in fibrinogen and prothrombin (p 463)

Heparin Titration

NORMAL RANGE—TECHNICAL NOTES Various modifications of Allen s method are used (10) Five ml of blood are added to 2000 gamma heparin One-half ml of the mixture is added to each of 10 tubes containing 80 to 260 gamma protamine sulfate in 20 gamma increments After 2 hours the end point is found this consisting of the lowest tube showing a solid clot Human blood normally clots in the 100 or 120 gamma tube (less than 3 25 gamma of heparin per ml of plasma)

CLINICAL CLUES *While there still exists considerable controversy as to the* frequency and importance of excess heparinoid activity this phenomenon has been demonstrated in certain thrombasthenic syndromes that are associated with clinical hemorrhage The beneficial effect of protamine and desoxycorticosterone in such instances might be dramatic (T–1290) Hyperheparinemia may also take place in patients exposed to ionizing radiation in leukemia in anaphylactic shock in the postpartum period and following nitrogen mustard therapy The concomitant presence of thrombocytopenia is variable

Acid Hemolysis (the Ham Test)

NORMAL RANGE—TECHNICAL NOTES Hemolysis of red cells is tested for at a slightly acid pH with carbon dioxide (19) One should observe if hemolysis occurs after incubation for 1 hour and centrifuging The blood sample should be *defibrinated*

Clotting Time and the Clot Observation Test

NORMAL RANGE—TECHNICAL NOTES Normal blood will clot in 4 to 12 minutes (Lee-White), and has a fibrinogen content of 200 to 400 mg per cent These tests should be performed in the fasting state (30)

CLINICAL CLUES Prolonged in hemophilia A and B, hyperheparinemia, afibrinogenemia, fibrinolysis and hypoprothrombinemia The clot observation test may be of value in diagnosing the fibrinogen fibrin conversion syndrome in pregnancy, as manifested by hemorrhage or shock (p 464) If no clot forms, the fibrinogen content can be assumed to be less than 60 mg per 100 ml of plasma Should a flimsy clot form which fragments and dissolves within 20 to 30 minutes, the concentration is probably less than 100 mg per cent (T-1291d)

Retraction Time of the Blood Clot

NORMAL RANGE—TECHNICAL NOTES Begins within 1 hour Marked retraction should be present by 18 hours

CLINICAL CLUES Poor retraction occurs in the various types of thrombocytopenia The results are apt to be misleading in the presence of marked anemia or polycythemia or fibrinolysis (p 679) Thrombasthenia is characterized by a normal platelet count but poor clot retraction

Prothrombin Time

NORMAL RANGE—TECHNICAL NOTES 12 to 15 seconds or 100 per cent of the control plasma (Quick one-stage method) A special oxalate tube is used It has been stated that the dilution of plasma in the Owren test eliminates the technical interference of heparin which occurs with the Quick test or any of its modifications using whole plasma In clinical anticoagulant practice, however the Quick method is preferable to some of the more refined methods since it actually serves as a ' battery" test for the total prothrombin related clotting mechanism

Plasma kept for longer than three hours use of excess anticoagulant during collection of blood, hemolysis u e of old thromboplastin extract or of calcium chloride not in an anhydrous state, retained soap or detergent in the glassware and improper technique, including failure to recognize the correct end point, are some sources of erros

CLINICAL CLUES Prolonged in vitamin K deficiency, dicoumarin (Dicumarol) therapy, "parahemophilia and SPCA (convertin) deficiency Sudden changes in the effect of Dicumarol on the prothrombin time can be induced by antibiotics (which may reduce the amount of endogenous vitamin K being made in the intestine)

Prothrombin Consumption Test

NORMAL RANGE Over 80 per cent of the prothrombin should be consumed in 1 hour

TECHNICAL NOTES The specimen must be collected in a special citrate tube and delivered promptly to the laboratory The exact time of the drawing is noted Prothrombin free human plasma should be used as the source of fibrinogen The degree of prothrombin consumption depends upon the available amounts of plasma thromboplastin, platelet enzyme and ' prothrombin accelerators

CLINICAL CLUES A considerably reduced ' consumption occurs in hemophilia, deficiency of the plasma thromboplastic component, hemophilioid disease, the presence of circulating anticoagulants and other hemorrhagic states This test may serve as a u eful diagnostic screening procedure (30)

globinuria (rarely) and in isoimmunization If agglutination occurs with both Rh positive and Rh negative cells, Rh antibodies can be excluded (T–706a)

Occasional false-positive tests are encountered in lupus erythematosus myeloma thalassemia idiopathic thrombocytopenic purpura, and with cold hemagglutinins The antiglobulin tests may be persistently negative in certain patients who demonstrate all the other features of autoimmune hemolytic disease (T–706b)

Red Cell Survival Studies

NORMAL RANGE—TECHNICAL NOTES Normal red cells transfused into normal recipients exhibit a survival of about 120 days with a linear slope of disappearance

CLINICAL CLUES In acquired hemolytic anemia (due to numerous causes) normal cells disappear rapidly in an exponential manner (T–706) Normal survival is found when disease is due solely to abnormalities in the red cells themselves as in congenital hemolytic jaundice

Macroglobulins (Screening Test)

NORMAL RANGE—TECHNICAL NOTES One or two drops of the patient s serum are placed into distilled water No precipitation occurs with normal sera A control test must always be simultaneously performed

CLINICAL CLUES The occurrence of a white precipitation in a patient with undiagnosed hepatosplenomegaly and bleeding phenomena should suggest macroglobulinemia (T–677 678) If positive the serum must be checked electrophoretically and by ultracentrifugation (See Proteins in Section II (p 692) False-positive and false-negative results have both been noted with this technique For example a Bence-Jones proteinemia could result in a positive serum drop test (T–676c)

OTHER STUDIES OF HEMOGLOBIN AND THE RED BLOOD CELLS

Hemoglobin

NORMAL RANGE—TECHNICAL NOTES Males—14 to 17 gm per 100 ml Females—12 to 16 gm per 100 ml

CLINICAL CLUES One may avoid iatrogenic anemia by appreciating the normally lower levels in females than in males

Volume, Packed Cells (Hematocrit)

NORMAL RANGE—TECHNICAL NOTES Males—42 to 50 per cent Females—40 to 48 per cent (A double oxalate tube is used and the specimen is centrifuged at 3000 revolutions/min for 20 minutes)

CLINICAL CLUES A most valuable and reliable guide in the study and therapy of anemia One may also obtain useful information from the buffy coat the color of the supernatant and the sedimentation rate (which can be performed in the same tube)

Measurement of Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration and Mean Corpuscular Diameter

NORMAL RANGE—TECHNICAL NOTES Volume 82 to 92 cu y (HCT × 10/R B C in millions) hemoglobin 28 to 32 yyg (gms of Hgb × 10/R B C in millions) hemoglobin concentration 32 to 36 per cent (gms of Hgb × 10/HCT) diameter 7 2 to 7 8 y

CLINICAL CLUES The supernatant of the centrifuged specimen is discolored if hemoglobinemia is present The test is positive in paroxysmal nocturnal hemoglobinuria It may be negative for various technical reasons, particularly multiple transfusions A positive result can be confirmed by the ability of thrombin to accelerate hemolysis of PNH cells (the Crosby test) (T-709)

Hemolysins

WARM HEMOLYSINS AND COLD HEMOLYSINS (THE DONATH LANDSTEINER TEST)

NORMAL RANGE—TECHNICAL NOTES Washed red cells from fresh defibrinated blood are incubated either at body temperature or are first chilled in ice for 20 minutes The tube should be examined for hemoglobin in the supernatant this must be done *before* warming when one is testing for cold hemolysins

See Section XVI for the Rosenbach test (p 826)

CLINICAL CLUES An occasional patient with hemolytic anemia will exhibit autoagglutinins at body temperature (T-805-808) In rare cases of syphilis cold agglutinins may be found, although a hemolytic anemia need not necessarily be present

Hemoglobinemia

NORMAL RANGE—TECHNICAL NOTES The presence of free hemoglobin in the plasma is detected by a pink or red color There is normally less than 5 mg per 100 ml in citrated venous blood The test is done with the benzidine reagent (Methemalbumin is also measured)

CLINICAL CLUES Hemoglobinuria usually occurs when the blood level exceeds 100 mg per cent (35) Levels over 50 mg per cent regularly occur in paroxysmal nocturnal hemoglobinuria They are also elevated following other causes of intravascular hemolysis

The Coombs Tests

DIRECT' TEST AND 'INDIRECT TEST

NORMAL RANGE—TECHNICAL NOTES The direct test is performed by mixing the patient s washed red cells with rabbit antihuman gamma globulin and observing for agglutination The indirect test is performed by mixing antihuman globulin serum with normal group O Rh positive and Rh negative red cells which have been incubated in the patient s serum Additional techniques with various media and proteolytic enzymes are occasionally helpful

Many variables relating to the specificity and potency of available sera (such as the contamination of the Coombs serum by bacteria or blood serum) the prozone phenomenon due to inadequate dilution insufficient washing of red cells and other technical errors may be encountered (T-707)

CLINICAL CLUES The Coombs test probably represents the most significant contribution to blood typing since Landsteiner s discovery of the ABO system Its value has been enhanced by the discovery of the newer antigens As an example antibodies for the antigens of the Duffy Kell and Kidd series often either fail to react with saline-suspended red cells or are not activated by albumin but do become manifest when Coombs serum is added (T-704a)

A positive 'direct' test indicates incomplete antibodies on the red cells this occurs in acquired and ' symptomatic hemolytic anemia paroxysmal cold hemo-

compatibility tests (since rouleau formation occurs due to the fibrinogen) At present there are 49 known human blood group factors or antigens belonging to at least nine genetically independent systems ' or ' families (T–704a)

See Section XVI for biologic cross match in suspected transfusion incompatibility (p 826)

CLINICAL CLUES The absence of serum isohemagglutinins in groups O A and B occurs in myeloma and in hypogammaglobulinemia (T–519) The inability *to type or cross-match blood properly should also make one suspicious of myeloma* All the newly discovered blood groups may be valuable in compatibility testing

The D antigen is the most important and immunologically variable one in the Rh system Erythroblastosis can occur on the basis of an ABO incompatibility although it is infrequent and less severe than that due to Rh incompatibility (T–704b)

Caution is suggested in attempts to correlate specific disease processes with the blood groups (T–1223) Wiener and others have discussed the medicolegal aspects of blood typing in detail (41)

Intestinal Absorption of Co^{60}–B_{12} of High Specific Activity (The Schilling Test) (18, 31, 32, 189) (T–1226)

NORMAL RANGE—TECHNICAL NOTES Absorption may be determined in several ways (1) measurement of the fecal excretion of radioactivity following an oral dose (2) measurement of the urinary excretion of radioactivity following an oral dose before and after intravenous nonradioactive B_{12} and (3) measurement *of the hepatic uptake following the tracer dose (with the scintillation counter directed* perpendicular to the liver) The abdominal counts are used as a control One can take counts over the liver as early as 48 hours after the administration of the tracer dose of radioactive B_{12} by removing the unabsorbed material with a cathartic and enema (18)

The various advantages and drawbacks of these methods have been reviewed by Glass (18) The development of $Co^{58}B_{12}$ which possesses a longer half life and greater radioactivity will probably permit a more ready determination of this material in the blood stream

CLINICAL CLUES A complete block to the intestinal absorption of vitamin B_{12} exists in pernicious anemia (both in relapse and in remission) after total gastrectomy and in sprue The mean urinary excretion in normal individuals is 13 3 per cent In patients with pernicious anemia it averages 0 85 per cent This technique is still experimental but it may be diagnostically *important in the differen*tiation of the macrocytic, nutritional and malabsorption anemias in the early diagnosis of sprue and in disturbed secretory activity of the gastric glands

The Schilling test is probably of greatest value in the diagnosis of pernicious anemia in patients with no apparent anemia (T–696) The normal urinary excretion of orally administered radioactive vitamin B_{12} (8 4 per cent or more) probably excludes pernicious anemia When results in the P A range are encountered renal disease must be considered In this instance however, there is no effect produced by intrinsic factor and the cobalt[60] labeled vitamin B_{12} is continually excreted *after the first 24 hours* (32)

There is impairment of the absorption of B_{12} in diabetics especially if a complicating retinopathy or neuropathy is also present (T–260b)

Color index (per cent Hgb /first two figures of R B C in millions × 2)

CLINICAL CLUES *Macrocytic anemias* occur in pernicious anemia, sprue, nutritional anemias, intestinal anastomoses, after total gastrectomy, hypothyroidism liver disease, and in aplastic anemia

Normocytic anemias are due to impaired blood formation (aplasia, toxins, infections, metastases) or to blood loss (hemolysis, bleeding)

Hypochromic anemias occur in iron deficiency, chronic infection, uremia, and thalassemia

Erythrocyte Sedimentation Rate (E S R)

NORMAL RANGE—TECHNICAL NOTES Wintrobe—males, 0 to 7 mm /hour, and females 0 to 15 mm /hour Westergren—males, 1 to 3 mm /hour, and females 3 to 7 mm /hour Test should be done promptly in a vertical tube and within a temperature range of 22° C to 27° C

The policy of "correcting for the sedimentation rate may occasionally prove to be misleading if an abnormal rate is "normalized" Even with a slow rate, however there may be metastatic disease or other severe organic disorders present (T-734b)

CLINICAL CLUES Useful as a screening test for inflammation in the body An unexplained elevation should direct attention to the possibilities of blood dyscrasias, neoplasms the collagen disorders, chronic infection localized suppuration, cryoglobulinemia, and macroglobulinemia It may be normal in sickle cell anemia and in brucellosis The sedimentation rate is increased in many viral infections as well as in infections caused by bacteria

It is still of great value in the management of acute myocardial infarction (It remains equally as valuable in this condition as the newer serum complement and C-reactive protein studies)(11) In the absence of other evidences of rheumatic fever activity following prolonged rest and treatment the elevation of the E S R *per se should* not be the basis for unnecessarily extending the period of complete rest

Paper Hemoglobin Electrophoresis (13) (T-716 718)

NORMAL RANGE—TECHNICAL NOTES Oxalated or heparinized blood should be used Distinctive electrophoretic mobility patterns occur with hemoglobins C and S using a phosphate buffer These migrate as positive ions (at different rates), in contrast to normal adult hemoglobin (A) which migrates as a negative ion While the abnormal hemoglobin F in thalassemia migrates closely with that of normal adult hemoglobin on filter paper electrophoresis the former can be separated by alkali denaturation

CLINICAL CLUES Hemoglobin C disease and its variants are suggested by the finding of target cells and splenomegaly in Negroes in the absence of sicklemia (p 196) This technique is also helpful in diagnosing the clinical variants of thalassemia and sicklemia It should be performed in Negro and Puerto Rican military personnel prior to their assuming permanent flying assignments No abnormality in the erythrocytes of congenital spherocytosis has as yet been found There is little or no increase in fetal hemoglobin in the thalassemia minor state

Blood Grouping

THE ABO SYSTEM AND THE RH-HR (CDE) SYSTEM (40, 41)

NORMAL RANGE—TECHNICAL NOTES Grouping sera must never be used unless they are proved to be potent at the time Plasma should not be used in

elevated serum protein Also elevated in parathyroid overactivity vitamin D excess excessive androgen and estrogen therapy Hodgkin s disease and extensive metastases (p 82) (T-311-313 316 1175) If elevated in the presence of an insulinoma look for multiple endocrine adenomata (T-52) Hypercalcemia without hypercalciuria or hyperphosphatemia occurs in the milk alkali syndrome (Burnett) (p 406) (1177 1178) Decreased in renal insufficiency, postparathyroidectomy states, osteomalacia acute pancreatitis steatorrhea and hyperthyroidism Low blood serum calcium levels in the presence of an abdominal crisis need not be indicative of acute pancreatitis since this finding has also been encountered in patients with mesenteric infarction small bowel obstructions and perforated peptic ulcer (T-1322c 1374a)

Carbon Dioxide Content and Combining Power

NORMAL RANGE 26 to 28 mM per liter in adults 20 to 30 mM per liter in children

TECHNICAL NOTES Serum The serum should be drawn without stasis under oil To calculate alveolar CO_2 and serum HCO_3 a serum pH should be done also

CLINICAL CLUES Important in both the diagnosis of metabolic and respiratory alkalosis or acidosis and for following the course of these disorders (62) Elevated with alkali ingestion vomiting and emphysema Decreased in uremia, diarrhea hyperpnea paraldehyde and methanol poisoning(T-242) and diabetes mellitus An elevated plasma bicarbonate may indicate the presence of potassium depletion even when the levels of the latter ion in the serum are apparently normal (T-304b)

Carotene

NORMAL RANGE Range of 70 to 250 microgm per 100 ml (Most normal individuals fall within the narrower range of 150 to 180 microgm per 100 ml) The level is influenced by diet liver disease and febrile states

TECHNICAL NOTES Plasma Readily performed with the colorimeter

CLINICAL CLUES This test has proved to be a most reliable screening guide in the diagnosis of the malabsorptive syndromes and in differentiating sprue from functional diarrhea (T-152) Levels of 30 to 70 microgm per 100 ml indicate moderate depletion they can be readily elevated if due solely to dietary factors Levels of 0 to 30 microgm per 100 ml indicate severe depletion of this fat-soluble vitamin and are found in steatorrhea they may rise with therapy Elevated levels occur in the hyperlipemias nephrosis diabetes mellitus hypothyroidism and the excessive ingestion of carrots in an attempt to improve vision

Chloride

NORMAL RANGE 100 to 106 mEq per liter

TECHNICAL NOTES Serum

CLINICAL CLUES Hyperchloremic acidosis occurs in the Fanconi syndrome lesions in the hypothalmus and third ventricle metabolic acidosis following the administration of chlorides or Diamox and aer ureterosigmoidostomies (T-306-309) Decreased in Addison s disease vomiting excessive diuresis the salt-losing nephropathies bronchogenic carcinoma(T-305b) and respiratory acidosis(T-23 304 305)

SECTION II

Blood Chemistries

Ammonia (see Section IV, p 715)

(see Section IV, p 715)

Barbiturate

NORMAL RANGE 0

TECHNICAL NOTES Serum Recent spectrophotometric determinations have proved simple and sensitive (61)

CLINICAL CLUES Coma level approximately 11 0 mg per 100 ml with phenobarbital and 1 5 mg per 100 ml with most other barbiturates

Bilirubin (van den Bergh Test)

NORMAL RANGE Direct 0 1 to 0 4 mg per cent Total 0 7 to 1 0 mg per cent (Indirect is total minus direct)

TECHNICAL NOTES It is the insolubility of the indirect form and *not* the nature of the protein binding which determines its failure to react in the diazo reaction without the addition of alcohol (50)

CLINICAL CLUES See Group III of Part I for an evaluation of obscure jaundice (pp 87 to 91) Constitutional hyperbilirubinemia is important to recognize if the other liver studies are relatively normal in the presence of chronic mild icterus (T–333) Indirect is usually more elevated in hemolytic jaundice "Direct is usually more elevated in obstructive and parenchymal jaundice

Bromide

NORMAL RANGE 0 33 to 1 73 mg per 100 ml

TECHNICAL NOTES Serum

CLINICAL CLUES The toxic level is 150 mg per cent (17 mEq /L) Chronic bromism should be considered in the presence of unexplained personality changes (p 64) (T–229 230)

Calcium

NORMAL RANGE 8 5 to 10 5 mg per cent (4 5 to 5 5 mEq per liter) (higher in children)

TECHNICAL NOTES Serum A serum protein should also be performed to indicate the relative proportions of bound and ionizable calcium

CLINICAL CLUES Elevated in sarcoidosis and myeloma due partly to the

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Cholinesterase (60)

NORMAL RANGE 0 44 to 1 54 pH units

TECHNICAL NOTES Serum This enzyme hydrolyzes acetylcholine into choline and acetic acid in the blood and body tissues

CLINICAL CLUES Plasma cholinesterase is produced by the liver Changes in its level tend to parallel those of the serum albumin In chronic or severe liver disease (cirrhosis, hepatitis, malignancy), the level is depressed The cholinesterase may also have some value as a prognostic aid It may also be depressed in hepatic amebiasis (even when the other liver function tests are not remarkable)(60c), mal nutrition and exposure to insecticides containing the organic polyphosphates Reports of high values in mysthenia gravis have been questioned

Citrate

NORMAL RANGE Fasting 2 0 ± 0 2 mg per 100 ml After citrated whole blood, the level may normally rise up to 16 mg per 100 ml

TECHNICAL NOTES Serum The serum calcium and protein should also be performed

CLINICAL CLUES Very high levels may occur during multiple transfusions particularly in the presence of disease of the liver or the hepatic circulation (T-1289 1290)

Congo Red Test

NORMAL RANGE More than 60 per cent is retained in the serum after 1 hour

TECHNICAL NOTES 10 ml of a 1 per cent solution should be injected intravenously Blood should be drawn after 4 and 60 minutes from the arm not used for the injection This test would best be avoided if many skin deposits are present (T-202) The test may be falsely positive if large amounts of the dye are excreted in the urine particularly in the presence of massive proteinuria

CLINICAL CLUES Primary and secondary amyloidosis may be diagnosed if 80 per cent or more of the dye is taken up by the tissues Potential reversibility exists if the suppuration or tuberculosis is controlled (T-201)

Creatinine (see Section III, p 698)

Cryoglobulins

NORMAL RANGE 0

TECHNICAL NOTES Serum The serum should be collected in a warm syringe and transported at 37 C Cryoglobulins may have to be distinguished from cryofibrinogens heparin precipitable cryofibrinogens, and cold agglutinins

CLINICAL CLUES These are abnormal globulins that have the physical characteristics of precipitating on cooling and redissolving with subsequent warm ing They may be found in severe Raynaud s syndrome acute hemolytic anemia myeloma, chronic lymphatic leukemia subacute bacterial endocarditis and kala azar (p 220) (T-805-808)

Fibrinogen

NORMAL RANGE 0 15 to 0 30 gm per 100 ml

TECHNICAL NOTES Plasma Collect as for the prothrombin content The addition of Fibrindex (Ortho) to a sample of oxalated blood is a potentially

useful semiquantitative method for determining the fibrinogen content Clotting should normally begin within 10 seconds or less (T–1291g)

CLINICAL CLUES Increased fibrinogen levels (350 to 1000 mg per 100 ml) are found during pregnancy or the menses, and in severe infections, malignancies rheumatic fever, rheumatoid arthritis, nephrosis, immunizations, and following radiation therapy Decreased levels occur in severe liver disease, severe malnutrition, congenital afibrinogenemia, and acquired afibrinogenemia or hypofibrinogenemia Also see 'Fibrinolysis under 'Hematologic Studies (p 679)

Glucose

NORMAL RANGE Fasting 70 to 120 mg per cent Post-prandial the levels should not exceed 180 mg per cent and should return to normal within 3 hours

TECHNICAL NOTES Whole blood An oxalate-fluoride bottle should be used The filtrate must be processed within two hours

The methods for determining the true blood sugar levels utilize filtrates that eliminate the effect of the nonglucose reducing substances which account for 20 to 30 mg per 100 ml of the determinations obtained by the Folin Wu method The Nelson method is very practical and accurate

The recent introduction of the Dextrotest kit provides a quick and relatively reliable method for the physician himself to determine the blood sugar level A concentrated and deproteinized blood filtrate is readily obtained by adding the venous blood sample (1 ml) to a 2 ml solution of sulfosalicylic acid and sodium bicarbonate (made by dissolving tablet P) and filtering The addition of tablet S creates heat and a characteristic color depending on the glucose content of the blood Levels of 100 150 or over 200 mg per 100 ml can then be ascertained from the blue olive green or brownish orange colors that develop (65e)

CLINICAL CLUES Also see Pancreas in Endocrine Studies (p 730) and Group II of Part I (p 70) If diabetes is suspected a postprandial blood test must be performed—even if no glucosuria occurs—since a high renal threshold may be present (T–255 256) Blood levels are also important in determining the insulin dosage when a diabetic nephropathy is present

An appreciation of the osmotic effects of hyperglycemia in the management of diabetic acidosis is of great importance in order to avoid excessive salt administration Since 36 mg per cent of excess glucose will exert an osmotic pull on the cells equivalent to 1 mEq NaCl a serum sodium of 140 mEq/L in the presence of a blood sugar of 360 mg per cent may actually be misleadingly low by 10 mEq/L (T–262)

Iron

NORMAL RANGE 50 to 200 gamma per cent (the higher levels occurring in males)

TECHNICAL NOTES Serum The technical margin of error is about 50 gamma per cent Scrupulous care is necessary to prevent contamination with the iron of reagents and glassware employed in the determination of serum iron levels

CLINICAL CLUES Hemochromatosis should be considered in the presence of atypical hepatomegaly or diabetes mellitus and after prolonged iron and transfusion therapy (p 60) (T–210-214) The levels may also be elevated in acute hepatitis—a potentially useful fact in distinguishing it from obstructive jaundice (The later onset of the maximum rise of serum iron in acute hepatitis suggests a more prolonged clinical course)(57) In spite of the actual increase in the body s iron stores low serum iron concentrations are obtained in a number of chronic diseases These include uremia carcinomatosis, and chronic infection (T–722)

Iron Binding Capacity

NORMAL RANGE Total capacity 250 to 300 gamma per cent Serum iron normally equals 20 to 50 per cent of the total capacity

TECHNICAL NOTES Serum must be freshly drawn in the fasting state

CLINICAL CLUES Complete saturation is diagnostic of hemochromatosis (T-210) Suspect this diagnosis in atypical liver disease and diabetes mellitus The total capacity may actually be reduced in hemochromatosis

Lipid Partition (45) (T-276)

TECHNICAL NOTES Fasting serum is required in all determinations

CLINICAL CLUES The reader is referred to the several discussions of deranged lipid metabolism in the text (pp 76 to 79)

CHOLESTEROL (TOTAL)

NORMAL RANGE 150 to 280 mg per 100 ml (The normal levels in the United States are considerably higher than in most other countries)

TECHNICAL NOTES The Sperry and Webb revision of the Schoenheimer Sperry method is much more accurate than the older Bloor method Elevated in all the hyperlipemias (since neutral fat carries cholesterol with it)

CLINICAL CLUES Normal in the histiocytic reticuloendothelioses Elevated in hypercholesterolemia myxedema (primary) biliary obstruction diabetes mellitus, and the nephrotic syndrome May be moderately elevated in coronary disease, with an increase in the C/P ratio and an increase in the S_f 12 to 400 classes of lipoproteins (45) Decreased in hyperthyroidism, renal insufficiency cachexia extensive liver damage, and steatorrhea

CHOLESTEROL ESTERS

NORMAL RANGE 50 to 65 per cent of the total cholesterol

TECHNICAL NOTES *Represents the difference between the total cholesterol* and the free cholesterol (color intensity measured without hydrolysis)

CLINICAL CLUES Reduced in severe liver damage Elevated along with the cholesterol in the various conditions cited above

PHOSPHOLIPIDS

NORMAL RANGE *220 to 400 mg per 100 ml as phosphorus, 9 to 16 mg* per 100 ml

TECHNICAL NOTES Calculated as 25 times the lipid phosphorus

CLINICAL CLUES The greatest increase (up to 3000 mg per 100 ml) occurs in xanthomatous biliary cirrhosis (T-319) Also elevated in uncontrolled diabetes mellitus myxedema the nephrotic syndrome, and the hyperlipemias Decreased in anemia and hyperthyroidism

TOTAL FATTY ACIDS

NORMAL RANGE 190 to 500 mg per 100 ml

TECHNICAL NOTES The Stern-Shapiro method for esterified fatty acids is simpler *and more rapid than the method for total fatty acids*

CLINICAL CLUES Elevated in essential and symptomatic hyperlipemia (T-281)

NEUTRAL FAT (TRIGLYCERIDES)

NORMAL RANGE 0 to 200 mg per 100 ml

TECHNICAL NOTES The serum concentration of triglycerides cannot be

measured directly It is calculated from the results of the total esterified fatty acids the phospholipids and the esterified cholesterol levels (and is subject to their cumulative errors) If elevated, the serum appears creamy

CLINICAL CLUES Elevated in hypothyroidism, glycogen storage disease (von Gierke) diabetes mellitus the nephrotic syndrome and the hyperlipemias Decreased in hyperthyroidism

LIPOPROTEINS (45)

NORMAL RANGE The serum lipids are almost always present in the plasma as constituents of lipoproteins On the basis of their physical and chemical characteristics two major classes of serum lipoproteins can be separated, (1) the low density or β-lipoproteins which contain over 80 per cent lipid and have molecular weights over 2 000 000 and (2) the high density or α lipoproteins which are only about 50 per cent lipid and have molecular weights of about 200 000

TECHNICAL NOTES The serum lipoproteins can be measured by the following methods by differential solubility by electrophoresis by ultracentrifugation immunochemically and turbidimetrically

CLINICAL CLUES In atherosclerosis and its related diseases, the low density lipoproteins tend to be increased in concentration—the rise being in any or *all of this group s subfractions However, the marked overlapping in the levels* of these patients with normals makes it impossible to predict accurately such complications as myocardial infarction and strokes (15b)

Magnesium (T–241)

NORMAL RANGE 2 05 ± 0 18 mEq per liter

TECHNICAL NOTES Serum is examined by the Garner modification of Kolthoff s titan yellow reaction with magnesium The development of a sensitive multichannel flame photometer for the determination of small concentrations of magnesium in the serum has overcome the difficulty posed by the intrinsically weak emission of this element in the serum (T–241c)

CLINICAL CLUES The clinical syndrome of magnesium deficiency consists of muscular twitchings and tremors choreiform and athetoid movements, convulsions and delirium in patients with alcoholism diabetic acidosis and others whose diet is devoid of this element (p 67) Decreased magnesium levels may also be found in the nephrotic syndrome cirrhosis lupus erythematosus and hyperthyroidism Since the deficit is primarily one of a cellular nature (as in the case of potassium deficiency) *a deficiency state may exist in the face of a spuriously high serum con* centration

Elevated levels may be encountered in uremia

Nonprotein Nitrogen (see Section III, p, 698)

Osmotic Pressure (see "Posterior Pituitary" in Section V, p 722)

Oxygen Saturation (Arterial)

NORMAL RANGE 96 to 100 per cent

TECHNICAL NOTES A syringe with heparin should be used

CLINICAL CLUES See Cardiovascular Pulmonic Function (p 784)

pH

NORMAL RANGE 7 35 to 7 45

TECHNICAL NOTES Serum collect under oil without stasis pack in ice

and deliver immediately Blood collect the same as for oxygen (Preferred for the evaluation of respiratory acidosis)

The determination of the pH of venous blood introduces many variables, most notably the rate of blood flow at the site of the venipuncture For the accurate determination of the arterial blood pH, the test should be performed within five minutes of the time the sample is drawn and must not be exposed to air Where a delay is unavoidable, glycolysis (*with the lowering of the pH by the liberation of* lactic acid) can be retarded for up to two hours by plunging the sample into ice at 0° C

CLINICAL CLUES May give conclusive information in evaluating, differentiating, and treating the various forms of acidosis and alkalosis (62) Elevated in metabolic alkalosis (excessive vomiting, bicarbonate intake) and respiratory alkalosis (hyperventilation) Decreased in metabolic acidosis (diabetic acidosis, renal failure methyl alcohol poisoning) and respiratory acidosis (emphysema narcosis) The spontaneous conversion of the initial respiratory alkalosis to a metabolic acidosis in salicylate poisoning may lead to much confusion (T–231)

Phosphatase, Acid (52, 58, 314)

NORMAL RANGE 0 5 to 3 5 units (King Armstrong) or 0 5 to 2 0 units (Gutman) total 0 0 to 0 6 units, prostatic

TECHNICAL NOTES Serum The serum should be drawn just prior to the analysis This enzyme splits monophosphate esters at an optimum pH of 4 0 to 5 0 It is very important that there be no hemolysis in the specimen since the different acid phosphatase found in red cells will give high levels

There are *various inhibitors that can be used to differentiate* between the erythrocytic acid phosphatase the prostatic" phosphatase, and the acid phosphatase originating from other tissues Inasmuch as the hepatic and the renal acid phosphatases are also sensitive to tartrate inhibition, the tartrate-inhibitable fractions cannot be regarded as specific for the prostatic acid phosphatase Nevertheless, there is a 10 to 100 1 excess of this particular fraction in adult prostate than in other human tissues

The more recent introduction of the relatively simple assay *of tissue acid phos*phatases in serum as an index of carcinomatous spread may constitute a great advance The copper ion is added to the substrate to inhibit the erythrocytic acid phosphatase (which constitutes about one half of the normal serum s ' total' acid phosphatase) (58b)

CLINICAL CLUES Markedly elevated in metastatic carcinoma of the prostate Slight elevations can occur in other metastatic malignancies following prostatic massage or infarction and in advanced Paget s disease A highly undifferentiated metastatic prostatic carcinoma may lose its biologic potential for producing large amounts of acid phosphatase, particularly after orchiectomy and estrogenic therapy (T–79b)

Elevations of the prostatic serum acid phosphatase level have been shown to be far more accurate than the total serum acid phosphatase levels in the diagnosis of prostatic malignancy, particularly when soft tissue or bony metastases are suspected (T–79c) Most human adenocarcinomas exhibit much greater acid phosphatase activity than does homologous mucosa or glandular tissue Consequently the assay of the tissue acid phosphatases in the serum with the copper inhibitory technique may be of great value in the diagnosis of extensive metastases, especially in the case of mammary carcinoma It may be of greater help in evaluating the response to hormonal and radiation therapy than are the much more limited urinary calcium activity studies (p 814)

Gaucher s disease can also produce very high concentrations of the serum acid phosphatase (i e , 10 3 and 8 3 units in two patients observed by Tuchman) (T–289)

Phosphatase, Alkaline

NORMAL RANGE 2 0 to 4 5 units (Bodansky) (Infants—up to 14 units adolescents—up to 5 units)

TECHNICAL NOTES Serum This enzyme breaks down monophosphate esters at an optimum pH of 8 0 to 9 0

CLINICAL CLUES Elevated in bone disease (Paget s disease rickets, osteomalacia), hyperparathyroidism biliary obstruction and occasionally in carcinoma of the liver (T–324) The level of the serum alkaline phosphatase in Paget s disease often falls if the patient is immobilized Decreased in hypophosphatasia (T–95)

Phosphorus, Inorganic

NORMAL RANGE 3 0 to 4 5 mg per cent (infants in the first year up to 6 0 mg per cent)

TECHNICAL NOTES Serum Must be fasting

CLINICAL CLUES Values above 5 mg per cent may be a good indication of excessive pituitary growth hormone secretion (T–98 99) Elevated in renal insufficiency hypervitaminosis D hypoparathyroidism pseudohypoparathyroidism, myeloma and Addison s di ease Decreased after the ingestion or infusion of carbohydrate, and in hyperparathyroidism osteomalacia rickets insulin therapy, sprue and disorders of the renal tubules including the Lignac Fanconi syndrome

Potassium

NORMAL RANGE 3 5 to 5 0 mEq per liter

TECHNICAL NOTES Serum Must not stand on cells more than one hour (flame photometer) Hemolysis of the blood sample and delayed separation of the serum from the cells could result in an erroneously high estimate of the plasma potassium concentration

CLINICAL CLUES Hypokalemia may correlate better with the electrocardiogram clinically than with the blood levels (T–291 292) Suspect low levels after diabetic coma prolonged suction or vomiting in chronic renal disease and after the prolonged use of steroids laxatives or enemas (T–293-298) Also decreased in primary aldosteronism and periodic paralysis (T–94 299) Hyperkalemia occurs in renal failure (particularly when K salts have been given) and in Addison s disease (See Group II of Part I pp 79 and 81)

A spurious hyperkalemia has been noted in patients with thrombocytosis in the absence of clinical potassium intoxication (378)

Protein (Chemical Analysis) (51, 55, 56)

TOTAL

NORMAL RANGE 5 0 to 8 0 gm per cent

TECHNICAL NOTES Serum preferably fasting BSP dye should be avoided (Lipemic or jaundiced sera may give falsely high results in the biuret determinations of total protein and therefore should be measured by Kjeldahl s methods)

CLINICAL CLUES Elevated in dehydration sarcoidosis myeloma lupus erythematosus myxedema and lymphogranuloma venereum The albumin fraction is mainly affected by such factors as malnutrition fever injury dehydration and edema

ALBUMIN

NORMAL RANGE 3 8 to 4 5 gm per cent
TECHNICAL NOTES Serum
CLINICAL CLUES Decreased in severe liver disease nephrosis, steatorrhea, starvation and amyloidosis

GLOBULIN

NORMAL RANGE 2 0 to 3 9 gm per cent (The older fractionation techniques using some variant of the Howe method separate some alpha globulin along with the albumin fraction This accounts for the lower limits of normal globulins—such as 3 0 gm per cent—that were cited in previous years)
TECHNICAL NOTES Calculated from the difference between the total protein and the albumin
CLINICAL CLUES Elevated in chronic liver disease, myeloma, lymphogranuloma venereum sarcoidosis lupus erythematosus kala azar subacute bacterial endocarditis macroglobulinemia and visceral larva migrans (p 186) (T-675 678) A marked reduction occurs in hypogammaglobulinemia ('agammaglobulinemia) but complete absence has not been found by reliable methods (p 145) (T-525 530) There is no correlation between the height of the serum globulin *per se* and the false positive serologic tests for syphilis that are encountered in many of these disorders

A/G RATIO

NORMAL RANGE 1 4 1 to 2 5 1
TECHNICAL NOTES This is a relatively valuable index provided that the albumin is not too low nor the globulin too high
CLINICAL CLUES This ratio may serve as a prognostic index in severe liver disease and in hypoalbuminemic states particularly following prolonged therapy

Protein (Electrophoretic Analysis) (43, 47, 53, 55, 56)

TECHNICAL NOTES Serum Separation can be variously performed by noting the mobility patterns in an electric field with a weakly alkaline phosphate buffer at pH 7 8 in a Tiselius cell or by the much simpler filter paper electrophoretic technique No method of zone electrophoresis yet devised has eliminated the problem of trailing (i e , the deposition of varying amounts of albumin along the supporting medium as this protein travels toward the electrode)
CLINICAL CLUES In an analysis of the serum protein distribution in 1516 admissions to a general hospital by the filter paper electrophoretic technique it was observed that (1) the most common abnormality was a decrease in the serum albumin concentration followed by elevations of the alpha 2 globulin gamma globulin, beta globulin and alpha-1 globulin components (2) increased levels of albumin and decreased levels of the serum globulins occurred rarely (3) the patterns may be pathognomonic for multiple myeloma, nephrosis and hypogammaglobulinemia (4) they may be useful in the diagnosis of hepatitis cirrhosis tuberculosis, sarcoidosis kala azar and lymphogranuloma venereum and (5) they may be of value in following certain patients with rheumatic fever rheumatoid arthritis malignancy infectious diseases and the sequelae of arteriosclerosis (47)

ALBUMIN

NORMAL RANGE 45 to 58 per cent of total protein
CLINICAL CLUES See clinical clues under Protein above

GLOBULIN

CLINICAL CLUES See clinical clues' under Protein above The globulin macromolecules may be found in the gamma beta and zeta zones (p 187) (T-677, 678)

NORMAL RANGE ALPHA 1 AND ALPHA 2 5 to 8 and 8 to 13 per cent of total protein

TECHNICAL NOTES ALPHA 1 AND ALPHA 2 More reliable than the chemical method

CLINICAL CLUES ALPHA 1 AND ALPHA 2 Decreased during the acute phase of hepatitis Elevated in fever chronic hepatitis and cirrhosis

NORMAL RANGE BETA 11 to 17 per cent of total protein

TECHNICAL NOTES BETA More reliable than the chemical method

CLINICAL CLUES BETA Elevated in xanthomatous biliary cirrhosis obstructive jaundice accompanied by hyperlipemia, nephrosis chronic hepatitis and cirrhosis

NORMAL RANGE GAMMA 11 to 20 per cent of total protein

TECHNICAL NOTES GAMMA Very helpful in graphically demonstrating hypergammaglobulinemia Electrophoretic pattern studies cannot detect levels of gamma globulin below 100 mg per cent with any degree of accuracy

CLINICAL CLUES GAMMA An M shaped pattern in myeloma is occasionally seen when graphed (T-674) Also elevated in the conditions cited above under globulin particularly striking in macroglobulinemia Markedly decreased in hypogammaglobulinemia and in the nephrotic syndrome

Salicylate

THERAPEUTIC RANGE 20 to 25 mg per cent

TECHNICAL NOTES Plasma Collect in heparin or oxalate

CLINICAL CLUES May be helpful in the diagnosis of acute salicylate poisoning (particularly in children) and in guiding therapy when large doses of the salicylates are employed (p 65) (T-231) Over 30 mg per cent for aspirin and over 5 mg per cent for sodium salicylate are considered toxic levels

Sodium

NORMAL RANGE 136 to 145 mEq per liter

TECHNICAL NOTES Serum Flame photometer method (*vide infra*)

CLINICAL CLUES Low in Addison s disease pulmonary infarction salt-losing nephritis the nephrotic syndrome following paracentesis and diarrhea (p 80) (T-22 23 179 303 305) The low sodium syndrome in cardiacs carries a much poorer prognosis than does primary chloride depletion (T-304) Elevated in prolonged nasogastric tube feeding Cushing s syndrome steroid therapy untreated heart failure (T-304h) and in lesions of the hypothalamus and third ventricle (p 82) (T-308) See discussion on pages 246–250

The normal levels for the serum sodium are probably wider than those hovering about 140 mEq /L In clinical medicine one not infrequently encounters levels of 130 mEq /L which are apparently not productive of symptoms but rather represent a biochemical adjustment at a lower osmostatic level (T-304b)

Sulfonamide

NORMAL RANGE 0

TECHNICAL NOTES Either blood or serum may be studied

CLINICAL CLUES Occasionally desirable and useful when a patient is on intensive therapy and has poor renal function

Spectrophotometric Patterns for

SULFHEMOGLOBINEMIA AND METHEMOGLOBINEMIA

NORMAL RANGE 0

TECHNICAL NOTES Heparinized blood, delivered immediately to the laboratory, should be used One should watch for the characteristic absorption in the red end of the spectrum A drop of 10 per cent NaOH will cause an immediate disappearance of the band if it is due to methemoglobin

CLINICAL CLUES Concentrations of 0 5 gm per cent of sulfhemoglobin and 1 5 gm per cent of methemoglobin will produce a degree of cyanosis equivalent to that of 5 0 gm per cent of reduced hemoglobin The test should be performed where severe cyanosis is present in the absence of convincing cardiac or pulmonary disease These states may occur in poisoning from excess nitrates or nitrites, aniline dyes sulfonamides and the various coal tar preparations (T-1390 1391)

Serum Glutamic Oxalacetic Transaminase (Aminopherase) and Related Enzyme Studies (Lactic and Malic Dehydrogenase) (48, 63) (T-1263m)

NORMAL RANGE 10 to 40 units

TECHNICAL NOTES This has become a comparatively simple and inexpensive spectrophotometric determination It may be performed on treated serum stored at 0 C for up to several days The test requires only five minutes to perform and produces comparable results in different laboratories

It is based on the characteristic absorption of radiation by diphosphopyridine nucleotide-hydrogenase-reduced coenzyme I, and the appearance or disappearance of reduced D P N due to dehydrogenation reactions

There must be no hemolysis when the SLD test is performed The determination of the SLD is a much less complicated procedure than that of the other enzymatic tests

In view of the universal distribution of the SGO T and the three glycolytic enzymes (viz isomerase lactic dehydrogenase, and aldolase) and the readiness with which they can escape from injured cells one must be cognizant of the many pitfalls associated with such biochemical indirect biopsy procedures

CLINICAL CLUES Elevations of the SGO T (and the other enzymes) probably are due to the leakage of this enzyme from areas of high concentration to areas of lower concentration A marked elevation within 12 hours occurs in acute myocardial infarction and characteristically declines by the sixth day (since large concentrations are present in the cardiac muscle) (48) A normal level is usually established within five days following a coronary operation (1263n) Experimental coronary insufficiency and pericarditis are not associated with any rise in SGO T activity, unless concomitant myocardial necrosis is also produced This test is also of particular value in the diagnosis of acute myocardial infarction when a left bundle-branch block exists or before electrocardiographic changes have occurred Only extremely high elevations of these enzymes following acute myocardial infarction carry poor prognostic implications

Even though the initial rise may not be as dramatic with the SLD as with the SGO T following acute myocardial infarction, the levels with the former appear to persist longer Unfortunately, this enzyme is more prone to become elevated following pulmonary embolism and other conditions within the chest The SGO T activity cannot be used as a specific test of cardiac injury in patients suffering bodily trauma, inasmuch as over 50 per cent of such injured patients may show elevated activity that is unrelated to demonstrable cardiac injury (49)

Significant elevations also occur in prolonged tachycardias of a very fast nature and in active rheumatic carditis However, aspirin can elevate the level in children with rheumatic fever

Another pitfall in the interpretation of the serum transaminase activity in suspected coronary disease is to be found in the prior administration of an opiate (T–869d) It would appear that this phenomenon is related in large measure to the acute spasm of the duodenum and of the biliary tract which may be induced in this manner Similarly an increased activity of this enzyme has also been encountered in patients with acute inflammatory disease of the pancreas

The failure of the serum transaminase to rise with pulmonary embolism can be used as an additional aid in differentiating it from myocardial infarction (46) If a rise occurs in pulmonary embolism it is usually of a much lesser degree and does not occur until the fourth day

This test is also a very sensitive indicator of hepatic inflammation, injury and metastases but little correlation has been noted with the other liver tests (63) A marked rise is consistently noted one to four weeks before other clinical or laboratory evidence of liver injury becomes apparent The serum transaminase *may be of considerable value in defining both the presence and the extent of* hepatic involvement in the nonicteric patient with infectious mononucleosis (T–731b) When both the transaminase and the alkaline phosphatase are elevated liver disease is definitely present On the other hand when the former is normal, an increased alkaline phosphatase is probably due primarily to bone disease Very little elevation of the SGO T follows abdominal surgery in which there had been little manipulation of the liver bed

The serum transaminase level may provide a relatively sensitive index of the rate and magnitude of active muscle destruction in certain primary myopathies (54) In myotonic dystrophy myasthenia gravis, and recent poliomyelitis however the levels are within normal limits

Urea (see Section III, p 698)

Uric Acid (64)

NORMAL RANGE 3 0 to 6 0 mg per cent (15 to 20 per cent lower in females)

TECHNICAL NOTES Serum Uric acid levels tend to decline in specimens which stand overnight Colchicine does not interfere with the nonmedication levels (as do probenecid salicylates and the steroids)

CLINICAL CLUES Elevated in gout, renal insufficiency leukemia and its treatment (p 184) polycythemia vera myeloid metaplasia myelofibrosis and the toxemias of pregnancy This test should be performed in all atypical cases of arthritis affecting males It may be a useful prognostic sign in the toxemias of pregnancy since hyperuricemia often precedes urea retention Elevated levels in patients with rheumatoid arthritis are sometimes attributable to the ingestion of small doses of salicylates Hypouricemia can occur in the presence of impairment of renal tubular reabsorption (as in the Fanconi syndrome and in Wilson s disease) (T–363)

Vitamin C (Ascorbic Acid) (376)

NORMAL RANGE 0 7 to 1 4 mg per 100 ml

TECHNICAL NOTES Fasting plasma is collected before clotting in lithium oxalate The microtitration method of Farmer and Abt is especially applicable to studies in children

CLINICAL CLUES Untreated scurvy is not encountered in the presence of detectable blood levels It requires six to eight weeks following its elimination from the diet before the level falls to zero (T-141) (Also see Section XIV, p 815)

Volume of Blood, Total (42)

NORMAL RANGE 8 5 to 9 per cent of the body weight (Males 69 ml/kg Females 64 ml/kg)

TECHNICAL NOTES *Serum* Inject 10 ml of 0 1 per cent Evans blue dye (T-1824) in saline intravenously Draw blood before, and 5 and 10 minutes after the injection from the opposite arm Allow for a mixing time of 15 minutes in the presence of shock or heart failure *Blood* The hematocrit (using a double oxalate tube) and the total protein may be indirect indicators

Although the Evans blue and I^{131} methods primarily measure the volume of distribution of albumin rather than the blood volume there is little diffusion of the plasma albumin before 10 minutes However as much as 15 per cent of both Evans blue and I^{131} labeled albumin may be adsorbed onto the glassware during the analysis

Where available the volume measurement with radioactive chromium tagged red cells obviates the objections to the T-1824 dye (namely, accession into the lymphatic space and saturation of the reticuloendothelial system) and to P^{32} (accession into the plasma space) Both the red cell mass and the plasma volume can be simultaneously determined with radioactive sodium chromate and chromic chloride (44)

Accurate results can also be obtained by injecting 20 microcuries or less of radioactive-iodinated human serum albumin (RISA or I*HSA) intravenously into one arm, and withdrawing a blood sample in 10 minutes from the other arm

CLINICAL CLUES *Increased in polycythemia vera heart failure* and pregnancy This determination may be helpful in differentiating polycythemia vera from the relative polycythemia due to a pathologically low blood volume (p 188) (T-681) Absolute erythrocyte volumes exceeding 60 ml per kg of body weight (dry technique) are unequivocally within the range of true polycythemia Decreased in shock dehydration prolonged illness and weight loss

SERUM AND PLASMA ELECTROLYTES

The flame photometer offers a convenient means by which the concentrations of electrolytes can be determined in the plasma and in the total extracellular fluid A brief technical review of this very important biochemical advance will probably be welcomed by many clinicians (65)(T-304b)

The serum, urine or any other body fluid to be studied is first diluted as desired (1 50, 1 200 etc) This aliquot is then poured into a funnel leading to a vaporizer that is controlled by a constant air pressure The specimen is vaporized into a flame in this manner within the apparatus The constancy of the flame is insured by the constant gas pressure and the supply of air

The various ions *impart different colors to their flames For example,* the sodium ion appears as a yellow flame whereas a purple color is imparted by the potassium ion Furthermore the intensity of the color is proportional to the concentration of

the electrolyte being studied In order to quantitate the concentration the color is converted into a current by means of its transmission through appropriate filters to a photoelectric cell The intensity of the color produced is accordingly proportional to the intensity of the flame s color (and therefore to the concentration of the electrolyte) The current created is readily measured by means of a galvanometer, and the concentration of the electrolyte in question arrived at very simply by a comparison of the color produced by the unknown with that produced by a standard concentration of the same electrolyte

Lithium is usually added to both the unknown and the control solutions most often as a 10 per cent concentration Since this element produces its own color and current it acts as an internal standard The resistance required to equalize the current produced by the unknown solution with that produced by the constant lithium solution is then measured With suitably prepared solutions it should be possible to obtain a degree of accuracy for sodium and potassium determinations by the internal standard technique that is within ± 1 5 per cent

The emission lines of calcium and magnesium are actually band spectra of oxide and are therefore not as intense as the atomic spectral lines of sodium and potassium Accordingly such a difference in the emission intensity makes it desirable to determine the calcium and magnesium at concentrations in the range of those normally present in the serum Nitric perchloric acid digestion and ashing of a small amount of the serum is required before atomization of the sample for calcium determinations (65c)

The flame photometer technique has been of incalculable help to the pediatrician in particular He is now able to cope intelligently with the many electrolyte problems posed by sick infants from whom only small blood samples can usually be submitted for analysis (65d)

CONVERSION TABLE FOR SERUM AND PLASMA ELECTROLYTES

ION	NORMAL VALUES	CONVERSION FACTOR	NORMAL VALUES
	(mg /100 ml)	(mg /100 ml. to mEq /L.)	(mEq /L = $\frac{\text{mg /100 ml.} \times 10}{\text{atomic weight}}$)
CATIONS			
Na	313 –333	0 43	136 –145
K	14 – 19	0 257	3 5– 5 0
Ca	9 0– 10 5	0 5	4 5– 5.3
Mg	1.2– 2 4	0 833	1 – 2
T tal			145 –157
ANIONS			
HCO (CO_2/v l%)	58 – 6	0 455	6 – 8
Cl	349 –371	0.286	100 106
HPO (mg P)	3 0– 4 5	0 58	2 – 3
SO (mg S)	1.6– 2 4	0 6 5	1 0– 1 5
Pr tein (gm /100 ml.)	6 5– 8 0	2.43	16 – 19
T tal			145 –157

SECTION III

Renal Function Tests—Urinalysis

BLOOD DETERMINATIONS

Creatinine

NORMAL RANGE 0 7 to 1 8 mg per cent
TECHNICAL NOTES Serum
CLINICAL CLUES Elevated in renal insufficiency except when acute or on an obstructive basis Although the serum creatinine rises somewhat later than the BUN it is less likely to be affected by such extraneous factors as the rate of diuresis and the protein intake

Nonprotein Nitrogen

NORMAL RANGE 15 to 35 mg per cent
TECHNICAL NOTES Serum (Fasting state particularly important)
CLINICAL CLUES This test is used as a crude estimation of glomerular function It may be relatively normal in advanced renal tubular disease, particularly if much water is consumed (T-174) It is elevated in uremia, hemorrhage (especially when into the bowel) dehydration and heart failure In certain cases with associated liver damage that is sufficient to impair urea synthesis the NPN may give a more accurate indication of the degree of azotemia than the BUN

Urea

NORMAL RANGE 12 to 25 mg per cent (as urea N) 25 to 52 mg per cent (as urea)
TECHNICAL NOTES Serum
CLINICAL CLUES Increased in uremia hemorrhage, fever, dehydration, and with an excessive protein intake Decreased in starvation, diuresis, and acute yellow atrophy of the liver A low BUN is not a necessary concomitant of hepatic failure, however, due to the dynamic relationship between urea synthesis and excretion *The finding of a very low concentration of urea in the urine may aid in the recognition of mild cases of acute tubular necrosis* (T-1281b)

URINE DETERMINATIONS

Albumin

NORMAL RANGE 0 to trace
TECHNICAL NOTES Heat and acetic acid test Nitric acid ring test Sulfosalicylic acid test Occasional false-positive tests may be caused by the gallbladder

and pyelography contrast media The use of the arylsulfonylureas in diabetes mellitus can produce false-positive tests for albumin when the sulfosalicylic acid test is employed

The results obtained with the simple tablet test for proteinuria (Albutest) are in good agreement with those derived from the sulfosalicylic acid precipitation method In this test the presence of protein is indicated by the development of a blue color when one drop of urine and two drops of water are added to the test tablet

CLINICAL CLUES Continuous proteinuria is evidence of organic renal disease (75) (T–173) It is present in acute and chronic nephritis, the nephrotic syndrome fever toxemia and drug and chemical poisonings Occasionally it may be postural Unexplained albuminuria in the presence of rheumatoid arthritis or chronic inflammation and infection should suggest secondary amyloidosis (T–198-202) Aminoaciduria is present in Wilson s disease and many other disorders (*vide infra*)

Aldosterone (see Section V, p 735)

Alkaptonuria

NORMAL RANGE 0

TECHNICAL NOTES If present the urine blackens when alkaline and on exposure to air Homogentisic acid can also be identified by the immediate appearance of a black spot when a drop of urine is placed on an exposed photographic film Although it may act as a reducing substance it is not fermented by yeast

CLINICAL CLUES Suspect ochronosis in the presence of these color changes particularly in cases of atypical arthritis or spondylitis (p 75) (T–273 274)

Aminoaciduria (T–195c)

NORMAL RANGE The urinary excretion of free amino acids normally accounts for only 1 to 2 per cent of the total urine nitrogen

TECHNICAL NOTES The concentration as well as qualitative identification of individual amino acids in the urine has been rendered possible in recent years with the advances in paper chromatography column ion-exchange chromatography and microbiological assay The amounts of the individual amino acids found in the urine reflect both their concentrations in the plasma and the degree of their reabsorption by the renal tubules

As a rule, glycine and histidine are less completely reabsorbed than the other amino acids While the aminoaciduria tends to be greater in individuals who consume high protein diets the amount of urinary amino acid excretion is not greatly increased by the ingestion of a protein meal *per se*

CLINICAL CLUES Aminoaciduria might variously result from either a disturbance of the metabolism of the amino acids that causes their concentration in the plasma to increase (as in the case of severe liver damage) or from defects in the renal tubular reabsorption mechanisms of the amino acids The defect in either instance may be limited to a specific amino acid or a small group of amino acids, or it may be generalized, involving most of the amino acids

The reader is referred to the discussions of phenylketonuria (p 569) cystinuria (p 422) cystinosis or the Lignac Fanconi syndrome (p 57) Wilson s disease(86) (p 100) glycinuria (p 422) and the general subject of renal aminoaciduria itself (p 58) in Part I Unusually large quantities of lysine arginine and ornithine—as well as cystine—are found in patients with cystinuria (T–1226b)

Aminoaciduria might prove to be a valuable test in the early diagnosis of intoxication due to a number of heavy metals, including lead, uranium, and cadmium

Amylase (see Section VII, p 756)

Arsenic

NORMAL RANGE Less than 0 04 mg per diem (even after the ingestion of fruit that has been sprayed with lead arsenate)

TECHNICAL NOTES A 24 hour specimen is required

CLINICAL CLUES The majority of patients with evidence of arsenical intoxication have values exceeding 0 1 mg per diem (T-250-252) Confirmatory evidence may be obtained at autopsy by an analysis of the hair or visceral organs (Levels exceeding 0 1 mg per 100 gm of hair are diagnostic)

Bile

NORMAL RANGE 0

TECHNICAL NOTES The foam test is sensitive It may be inaccurate however, if the patient is receiving penicillin streptomycin PSP, riboflavin, or atabrine The Ictotest (bilazo) the Harrison spot test (barium impregnated strip) and the Franklin test (Fouchet s reagent) can all be conveniently performed now

CLINICAL CLUES Bilirubinuria is an extremely sensitive indicator of liver disturbance or biliary obstruction

Boric Acid (T-1186)

NORMAL RANGE 0

TECHNICAL NOTES After acidifying the urine with concentrated hydrochloric acid freshly prepared turmeric paper is dipped into the solution and then dried in air The appearance of a pink to red color denotes the presence of boric acid A rapid confirmatory test consists in the placing of a drop of concentrated ammonia water on the tested paper A transient blue-black color confirms the presence of boric acid

Recent quantitative colorimetric methods for determining trace quantities of boric acid are now available and obviate the false-positive turmeric reactions (T-1185)

CLINICAL CLUES This determination may help in the recognition of the milder cases of boric acid intoxication particularly when the diagnosis of Ritter s disease is entertained In addition to its qualitative presence in the urine the diagnosis of boric acid poisoning should also rest on the finding of toxic concentrations of this substance in the blood or tissues

Calcium

NORMAL RANGE Under 150 mg per diem

TECHNICAL NOTES A 24 hour specimen is analyzed following a diet that has been free of milk products for three days It is collected in a special bottle with HCl (Also see Parathyroid Studies in Section V for the Sulkowitch test, p 725)

CLINICAL CLUES Increased in hyperparathyroidism diuresis, acidosis, vitamin D excess the Fanconi syndrome sarcoidosis (T-748) and extensive osseous metastases (Hypercalcemia usually does not occur until the urinary calcium ex

ceeds 500 mg daily When 1 gm of bone is destroyed by neoplastic tissue about 100 mg of calcium are liberated and excreted in the urine)(T-310-313) Decreased in hypoparathyroidism, hypothyroidism, renal insufficiency, steatorrhea vitamin D deficiency diarrhea, and the milk alkali (Burnett) syndrome

Catechols (see Section V, p 732)

Chloride

Normal Range Over 50 mEq per liter (10 to 15 gm per diem)

Technical Notes A modified Fantus or Schales method can be readily adapted for bedside use Testing an aliquot of the 24-hour collection is more accurate in computing the total loss It is also useful in following patients on low salt diets and with fluid-electrolyte problems (83b)

Clinical Clues Increased in renal insufficiency diuresis high chloride intake, adrenocortical insufficiency and acidosis Decreased in dehydration alkalosis restricted chlorides vomiting and the Cushing syndrome The urinary chlorides may not accurately represent the actual behavior of the body sodium when patients are consuming chloride in combination with cations other than sodium

Chorionic Gonadotropin (see Section V, p 726)

Coproporphyrins (Types I and III)

Normal Range 50 to 250 microgm per diem

Technical Notes A 24-hour specimen is collected with 5 gm of sodium carbonate These substances do not react to Ehrlich s reagent The degree of red fluorescence under ultraviolet light or the absorption spectrum is studied The urine itself appears normal when the level is increased

Clinical Clues A very effective method for screening lead poisoning suspects (T-235)

Copper

Normal Range 1 5 to 5 microgm per 100 ml

Technical Notes A screening test with diethyldithiocarbonate followed by amyl alcohol extraction is currently being used

Clinical Clues Markedly increased in Wilson s disease (T-363 364) Also increased in certain mental disorders (86)

Creatine

Normal Range Under 100 mg per day (or less than 6 per cent of the creatinine) In children under one year it may equal the creatinine In other children up to 30 per cent of the creatinine value is normal

Technical Notes A 24 hour specimen is preserved with toluol

Clinical Clues Increased in hyperthyroidism, starvation myositis the various muscular atrophies myasthenia gravis and while on a high creatine diet Decreased in myotonia congenita

Creatinine

Normal Range 15 to 25 mg per kg of body weight

Technical Notes A 24-hour specimen is preserved with toluol

CLINICAL CLUES Increased in familial periodic paralysis Decreased in renal insufficiency and myotonia congenita

Fat ("Sizzle Test") (84)

NORMAL RANGE No sizzling or popping is normally present

TECHNICAL NOTES Scuderi's "sizzle test" consists in removing the top layer of urine with a platinum wire loop and putting it into a Bunsen flame

CLINICAL CLUES Sizzling or popping occurs if fat is present in dilutions up to 1 1600 In one report 30 patients with extensive bony trauma had positive sizzle tests, but only 19 of these also showed enough microscopic fat to support a diagnosis of fat embolism (Also see p 216)

Hemoglobinuria (72) (T-709)

NORMAL RANGE 0

TECHNICAL NOTES Centrifuged urine The benzidine test or spectrophotometry are employed If hemoglobinuria from various causes is present the supernatant will remain discolored It must be distinguished from other causes of red urine particularly porphyria excess urobilin beet pigment, diagnostic chemicals (phenolphthalein, Congo red), drugs (antipyrine, pyridium), alkaptonuria melanin pigments hemosiderin, methemalbumin, and myoglobinuria Careful spectroscopy the absence of plasma discoloration, and muscle biopsy will differentiate idiopathic paroxysmal myoglobinuria from hemoglobinuria (p 194) (T-710) See Section XVI for the Rosenbach test (p 826)

CLINICAL CLUES Hemoglobinuria is indicative of excessive hemolysis such as may occur with incompatible blood transfusions paroxysmal nocturnal hemoglobinuria favism, malaria, paroxysmal cold hemoglobinuria march hemoglobinuria, and chemical poisonings

Hydroxyindoleacetic Acid (a Serotonin Metabolite)

NORMAL RANGE 0

TECHNICAL NOTES Pyridium mephenesin, and PSP produce nonspecific color changes, but not the positive purple color Chlorpromazine tends to interfere with the color reaction for serotonin metabolites

CLINICAL CLUES Marked elevations are suggestive of metastatic argentaffinoma (T-1073) Elevations in the excretion of 5-hydroxyindoleacetic acid in the urine have followed the administration of reserpine and Sparine (1073d)

17 Hydroxycorticoids (see Section V, p 734)

17-Ketosteroids (see Section V, p 732)

Lead

NORMAL RANGE May be found in amounts up to 0 08 microgm per ml or 120 microgm total per diem in healthy adults

TECHNICAL NOTES 24-hour specimen

CLINICAL CLUES Suspect plumbism where vague gastrointestinal, nervous, and neuritic complaints occur in an individual with the appropriate occupational background (p 65) (T-233-236) The urinary coproporphyrins are also helpful as a screening test in cases of suspected lead poisoning (T-235)

Osmotic Pressure (see "Posterior Pituitary" in Section V, p 722)

pH

NORMAL RANGE 4 8 to 7 8

TECHNICAL NOTES Nitrazine paper gives an accuracy of within 0 3 units of pH The urine must be fresh and have no acid preservative added

CLINICAL CLUES Increased in diuresis alkalosis primary aldosteronism, hyperventilation, after meals and with infection caused by certain urea splitting bacteria Decreased in acidosis shock oliguria and some urinary tract infections

Porphobilinogen (T-217, 218)

NORMAL RANGE 0

TECHNICAL NOTES A freshly voided specimen is essential The Watson Schwartz modification of the Ehrlich reaction for urobilinogen is used Also observe for the characteristic fluorescence under ultraviolet light

CLINICAL CLUES Suspect porphyria in the presence of atypical abdominal pain polyneuritis and sunlight sensitivity Even if porphobilinogen is present, the urine may be colorless in a freshly voided alkaline specimen A characteristic pink to red fluorescence under ultraviolet light occurs when it is present Porphobilinogen is sometimes also found in liver disease lymphoma malignancy and in the course of some infectious diseases

Potassium

NORMAL RANGE 1 5 to 3 0 gm per diem

TECHNICAL NOTES 24-hour specimen Flame photometry

CLINICAL CLUES Excessive loss of this electrolyte occurs in certain cases of chronic nephritis primary aldosteronism diuresis increased dietary intake drug usage familial periodic paralysis and Cushing s syndrome (T-291 293) Decreased in Addison s disease dehydration and renal insufficiency

Protein (76)

ALBUMIN (SEE ABOVE UNDER ALBUMIN)

QUANTITATIVE (74 76)

NORMAL RANGE 20 to 80 mg per diem

TECHNICAL NOTES A 24-hour specimen should be preserved with toluol and refrigerated Since hyaline casts and red blood cells dissolve in dilute urines especially if alkaline the specific gravity may have a considerable bearing on the rate of proteinuria

CLINICAL CLUES Occasionally useful in evaluating the course and the effect of therapy in the nephrotic syndrome and in amyloidosis

BENCE-JONES

NORMAL RANGE 0

TECHNICAL NOTES A fresh urine specimen is necessary When present the protein precipitates between 50 and 56 C and redissolves at boiling A simple screening test for the presence of Bence-Jones protein consists in overlaying the urine with several ml of concentrated hydrochloric acid If no white ring develops

at the interphase this protein is not present It should be realized that the presence of marked albuminuria renders identification of the Bence-Jones protein very difficult (T-672a)

CLINICAL CLUES This protein is infrequently observed in conditions other than myeloma (T-671) It has been found, however, in the adult Fanconi syndrome (due to the aminoaciduria with much methionine), metastatic carcinoma to bone, macroglobulinemia, senile osteomalacia leukemia, and hyperparathyroidism (T-79a) There is no apparent correlation between the type of abnormal serum component or the composition of the urinary protein components and the presence or absence of this particular protein (76)

ELECTROPHORESIS

NORMAL RANGE 0 (Two very small components due to mucoproteins may normally be found)

TECHNICAL NOTES A fresh urine specimen is necessary Mobility patterns are studied at a pH of 8 6

CLINICAL CLUES Performed by interested investigators when myeloma is suspected because of the unique major motility component in the gamma globulin range in this disorder Interesting albumin and globulin patterns are also found in nephritis, amyloid nephrosis lupus erythematosus and intercapillary glomerulo sclerosis (76)

Sodium

NORMAL RANGE 3 0 to 5 0 gm per diem

TECHNICAL NOTES 24 hour specimen Flame photometry

CLINICAL CLUES Increased in diuresis, Addison s disease renal insufficiency, and after meals Decreased in the low sodium syndrome dehydration, diarrhea cardiac failure the nephrotic syndrome and renal insufficiency Suspect a salt losing nephritis' in the presence of ' Addison s disease with hypertension (p 52) (T-22, 23 179)

Sugar

GLUCOSE

NORMAL RANGE 0

TECHNICAL NOTES The Clinitest or Galatest methods are the most convenient and accurate for general use For quantitative studies examine a 24-hour or a divided 24 hour specimen collected with toluol and refrigerated Check with blood sugar levels

Although an opaque green Benedict reaction usually is of no significance only repeat tests and fermentation studies can conclusively prove this (89) The use of the specific enzyme paper preparations presently available for testing urinary sugar quantitatively may give erroneous results This is particularly apt to be the case when more than 0 1 per cent glucosuria is present (T-263b)

CLINICAL CLUES Glucosuria may occur in diabetes mellitus Cushing s syndrome renal glucosuria and acute or chronic pancreatitis

Many patients with 'nondiabetic glucosuria during glucose tolerance tests ultimately will prove to be true diabetics and accordingly should be retested

NONGLUCOSE REDUCING SUBSTANCES (78)

NORMAL RANGE 0

TECHNICAL NOTES A freshly voided specimen without a preservative should be used The following procedures may be utilized in clarifying cases of persistent normoglycemic melituria (1) Reduction of copper solutions in a few to several hours at room temperature or within 10 minutes at 50 to 60 C is produced by the ketosugars (as pentose and fructose) (2) Fermentation test (see below) (3) The Bial test which is positive for pentose (4) The Seliwanoff test which is positive for fructose (5) Preparation of the characteristic osazones with phenylhydrazine (methylphenylhydrazine for fructose) (6) Paper enzyme tests (Tes-Tape Clinistix) which are specific for glucose The Galatest is particularly sensitive to traces of formaldehyde

CLINICAL CLUES May be due to pentosuria fructosuria (T-257) lactosuria pregnancy ochronosis and various drugs (cinchophen salicylates aminopyrine streptomycin) It is unwise to assume that reductions in pregnant patients are due to lactose Since the paper test material for sugar is impregnated with glucose oxidase it can be used as a specific test for glucose when the question of lactosuria fructosuria, or pentosuria arises (109)

FERMENTATION TEST FOR DOUBTFUL REDUCTIONS (88)

NORMAL RANGE No glucose

TECHNICAL NOTES Ferment in an open test tube within a water bath at approximately 96 F for 10 to 15 minutes Use equal parts of urine (5 ml is sufficient) and baker s yeast Centrifuge and repeat the test

CLINICAL CLUES All the glucose that gives a green Benedict reaction is destroyed in this process Pentose is not fermented

Toxic Chemicals (Mercury, Arsenic, Nickel Cadmium, etc)

NORMAL RANGE 0

TECHNICAL NOTES Whenever poisoning is suspected save all the body excretions for analysis

CLINICAL CLUES Suspect poisoning in the presence of unexplained skin liver, nervous system and bone marrow derangements Concentrations of mercury in excess of 0 25 mg per liter of urine are indicative of excessive exposure to this substance (T-246) (Also see above under Arsenic)

Urobilinogen

NORMAL RANGE Up to 1 0 Ehrlich units or positive in up to a 1 20 dilution

TECHNICAL NOTES A 2-hour sample is collected preferably between 1 and 3 p m

CLINICAL CLUES Valuable in the diagnosis and observation of jaundice and biliary tract disease Urinary urobilinogen may occur in obstructive jaundice if a cholangitis is present *above* the obstruction It also serves as a useful screening test for the presence of porphyrins

Uropepsin (see Section VII, p 754)

Volume

NORMAL RANGE 1000 to 1500 ml

CLINICAL CLUES Increased in diuresis polydipsia diabetes insipidus renal

at the interphase, this protein is not present It should be realized that the presence of marked albuminuria renders identification of the Bence-Jones protein very difficult (T-672a)

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CLINICAL CLUES Glucosuria may occur in diabetes mellitus Cushing s syndrome, renal glucosuria and acute or chronic pancreatitis

Many patients with nondiabetic glucosuria during glucose tolerance tests ultimately will prove to be true diabetics and accordingly should be retested

Casts (Hyaline, Epithelial or Granular, Blood, Waxy)

Technical Notes These structures usually originate in the tubules distal to the loop of Henle Precipitation of protein is dependent upon the nature and concentration of the proteinuria the pH in the tubules, and the concentration of the dialyzable solutes Normal Addis count (12 hours) 0 to 9300 (1000 average)

Casts disintegrate rapidly in dilute alkaline specimens this is accelerated if bacterial growth is allowed to take place When renal failure prevents the concentration or acidification of the urine, the addition of NaCl crystals or a few drops of concentrated HCl can prevent cast dissolution

Schreiner has presented a good review of both the examination and classification of casts and their clinical correlations (82)

Clinical Clues Hyaline fatty and granular casts are indicative of nephron degeneration Blood casts are seen in glomerulitis, the collagen disorders and embolism Broad or renal failure' casts herald uremia Waxy casts are related to the length of time the urine remains in the tubules

The width of casts is a valuable index of tubular atrophy and dilatation since the broadest casts are derived from the dilated nephrons associated with parenchymal scarring The density of the granules in casts is a function of their age

White blood cell casts may be the only evidence of an underlying pyelonephritis The finding of these pus casts in the urine (often incorrectly reported as ' clumps of pus cells by technicians) is an important clue to the presence of asymptomatic pyelonephritis

"Telescoped" Urine

Technical Notes Varying combinations of all the cellular elements (red blood cell casts double refractile oval fat bodies renal failure casts) with proteinuria are indicated by this designation

Clinical Clues These combinations are occasionally noted in chronic nephritis and the collagen disorders (especially polyarteritis) (T-185 950) Proteinuria casts and red cells also occur simultaneously in paroxysmal hemoglobinuria and angiokeratoma diffusum (T-709 821)

Hemosiderin

Technical Notes May occur as highly refractile yellowish brown granules either in the sediment or in the renal epithelial cells Also detected by the Prussian blue reaction or as jet-black particles when one drop of 30 per cent ammonium sulfide is added (due to the formation of ferric sulfide) (72)

Clinical Clues Hemosiderinuria may be a sign of hemoglobinuria or of methemalbuminemia even when hemoglobin is absent from the urine

Crystalluria

Technical Notes *Usually of little clinical significance* In an acid urine uric acid and calcium oxalate crystals are most commonly found The amorphous urates will dissolve with heat In an alkaline urine phosphate crystals are the most common they can be dissolved in acetic acid Double refractile bodies are best seen with polarized light

Clinical Clues Occasionally useful in following patients with renal lithiasis and gout Leucine and tyrosine crystals may be clues to the presence of atrophy of the liver Unique crystals due to the sulfonamides, cystine and those of hemo-

insufficiency, and diabetes mellitus (p 721) Decreased in dehydration, urinary obstruction, the low salt syndrome, shock, heart failure, and the nephrotic syndrome

URINE SEDIMENT (77)

General

TECHNICAL NOTES Scribner *has advocated the study of the superconcentrated* urinary sediment in puzzling instances of possible renal disease, particularly when minimal hematuria and orthostatic albuminuria are encountered In his technique, the sediment is allowed to settle in the entire overnight specimen It is then separated from the supernatant liquid and centrifuged until a "button" is obtained The latter is then placed either on a counting chamber or on a slide, but without a cover slip (in order to avoid dispersing the sediment) (83a)

CLINICAL CLUES It should be appreciated that the Addis count has little clinical significance This study is limited primarily to the serial quantitative evaluation of the extent of renal damage, and the changes in the nephropathy that occur as a result of therapy

Red Blood Cells

TECHNICAL NOTES Red cells must not be confused with yeast cells or urate crystals The benzidine test is not usually helpful Normal Addis count (12 hours) 0 to 1,500 000 (65,000 average) Occult blood in the urine can also be detected by a sensitive chemical test (An Occultest tablet is added to a filter paper square containing a drop of the urine specimen A blue color on the paper within a few minutes usually indicates hematuria)

Prostatic spherules may be mistaken for red blood cells Their smaller size, the absence of biconcavity and crenation, their persistence after the addition of acetic acid *and their abundance in the prostatic secretions aid in this differen*tiation

CLINICAL CLUES The absence of hematuria is an important criterion for recovery in acute nephritis (T-173) When red blood cells are seen within casts one can be sure that the bleeding is originating from the kidney tubules Sudden hematuria with back pain or shock should suggest a renal infarct (arterial or venous), or an acute dissecting aneurysm

Chronic asymptomatic hematuria is occasionally noted in telangiectasia the sickle cell disease or trait (T-711-713), angiokeratoma diffusum (T-821), and 'congenital hereditary hematuria' (p 423) (T-1246, 1247) See Part I for discussions of asymptomatic microhematuria (p 223)(T-814), 'athletic pseudonephritis" (p 223)(T-815), and radiation nephritis (p 399) (T-1201)

White Blood Cells

TECHNICAL NOTES Should be distinguished from red cells, yeasts and urate crystals (see below) Normal Addis count (12 hours) 32,000 to 4,000 000 (320,000 average) The two-glass test may be useful in locating a lower genitourinary tract infection causing pyuria particularly prostatitis

CLINICAL CLUES *Pyuria is frequently intermittent It is present* in only 25 per cent of patients with perinephric abscess When pyuria is present without proteinuria, the renal parenchyma is probably not involved See Part I for a discussion of the very important subject of pyelonephritis (p 109)

Casts (Hyaline, Epithelial or Granular, Blood, Waxy)

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CLINICAL CLUES Occasionally useful in following patients with renal lithiasis and gout Leucine and tyrosine crystals may be clues to the presence of atrophy of the liver Unique crystals due to the sulfonamides, cystine and those of hemo

chromatosis occur Free and intracellular birefringent bodies are found in angiokeratoma diffusum (T–821) Double refractile bodies are encountered in nephrosis and in visceral angiitis

Cancer Cells (see "Exfoliative Cytology," p 790)

Yeast Cells

TECHNICAL NOTES Distinguished from red cells by their insolubility in acids and alkalis their ovoid shape their lack of color, the variability in size, and the budding growth

CLINICAL CLUES These organisms are most commonly noted in females and in diabetic patients

Bacteriuria

TECHNICAL NOTES The urine should be collected in a clean bottle (with a little formalin if the examination is deferred) (See Section VI for bacteriology, p 737) Clean voided urine specimens can be studied with considerable accuracy after careful preparation of the labia or penis without incurring the dangers of iatrogenic urinary tract infection due to catheterization

CLINICAL CLUES This is an important and frequently neglected examination Bacteriuria may actually be more significant than pyuria For practical clinical purposes the gram stain of the freshly collected and unsedimented urine will differentiate contamination from infection (T–398) In the absence of treatment low colony culture counts (i e 1000 to 2000 per ml) are usually indicative of bacteriuria resulting from contaminants The reduction in the number of colonies several days following therapy is often a valuable indicator of the efficacy of such medication

"Glitter Cells"

TECHNICAL NOTES Sternheimer s stain is added to one drop of the urinary sediment White blood cells with specifically stained nuclei, cytoplasm and cytoplasmic granules showing much Brownian movement are looked for Although the Brownian movement can be readily seen in unstained preparations with ordinary microscopy the use of the Sternheimer Malbin supravital stain (gentian violet and safranine) makes it possible to recognize abnormal nuclear-dye absorption It also facilitates recognition of all the other formed elements (85)

CLINICAL CLUES These findings are highly suggestive of pyelonephritis but are not always present in typical cases The glitter cell phenomenon is by no means pathognomonic of renal infection since it has been encountered in acute and chronic glomerulonephritis cystitis other renal diseases and in urine contaminated with prostatic fluid vaginal secretions and trichomonads (66) The repeated absence of these cells in the urine sediment is usually evidence against a pyelonephritis

Epithelial Cells

TECHNICAL NOTES It may be difficult to distinguish these cells from white blood cells

CLINICAL CLUES Usually enough degeneration has occurred to prevent the accurate establishment of their origin from either the tubules or the lower urinary tract Renal tissue found in the urine of a seriously ill diabetic patient may give confirmatory evidence of a necrotizing papillitis (T–393-396)

Oval Fat (Lipoid) Bodies (Birefringent Droplet Containing Epithelial Cells)

TECHNICAL NOTES Oval fat bodies are best studied by adding 1 drop of gentian violet stain and 2 drops of Sudan IV stain to the sediment Birefringent droplets are best seen by the micropolaroscopic technique in an acidified urine

CLINICAL CLUES If specifically sought for these bodies can be frequently found in patients with intercapillary glomerulosclerosis and chronic glomerulo nephritis (81) They are also noted in systemic diseases affecting the kidney espe- cially the collagen hypersensitivity group (80)

Fat

TECHNICAL NOTES Round droplets are present which appear black under *low power and with subdued light (One should be sure they are not due to an* unclean collecting utensil or to an oiled catheter) The top layer of the last voided specimen should be examined Osmic acid and Sudan stains are usually not neces- sary If used, the Sudan IV must be fresh highly concentrated, and should be allowed to act for at least five minutes on the slide

CLINICAL CLUES Fat droplets may be noted after the third day in fat *embolism They have also been found in a large number of patients with fractures* who exhibit no other evidences of fat embolism (p 216) (T–792 796) (Also see Sizzle Test above)

RENAL FUNCTION STUDIES (68, 69, 71)

Specific Gravity

NORMAL RANGE 1 002 to 1 040

TECHNICAL NOTES One per cent albuminuria (10 gm per liter) will raise the specific gravity by only 0 003 The failure of the specific gravity in patients without evident renal disease to rise to normal values in response to dehydra *tion can be due to the antecedent ingestion of a low protein diet Similarly* maximal osmolar concentration of the urine (estimated by the freezing point) is greatest after a high protein diet

CLINICAL CLUES Increased in dehydration cardiac failure diabetes mel litus and after epsom salts or iodine-containing contrast media Decreased in renal insufficiency diuresis and diabetes insipidus In the presence of edema low specific *gravity values do not necessarily indicate renal damage No matter how small the* volume of urine produced the patient with acute renal failure is unable to con centrate urine appreciably (T–180c)

Dilution Concentration Test

NORMAL RANGE *Normal kidneys should dilute to 1 004* (–) and concen trate to 1 025 (+)

TECHNICAL NOTES Abstinence from liquids for at least 16 hours is neces- sary followed by the ingestion of adequate amounts of water Attempts to test the concentrating ability by means of fluid restriction are contraindicated in the presence of frank azotemia

CLINICAL CLUES The patient *with extensive renal disease and marked* tubular damage particularly of the distal tubules is unable to concentrate urine (this being the first function usually lost) or to dilute urine

Phenolsulfonphthalein (PSP) Test

NORMAL RANGE Excretion of at least 25 per cent by 15 minutes, 40 per cent by 30 minutes, and 60 per cent by 120 minutes

TECHNICAL NOTES Adequate hydration for 30 minutes before the test is essential One ml of the dye is injected intravenously The total urine is collected 15, 30, and 120 minutes after the injection The patient should *not* void just prior to injection of the dye, since a partially full bladder renders the 15 minute specimen easier and more accurate

CLINICAL CLUES This is a test of the function of the proximal convoluted tubules and of the effective renal blood flow Increased in fever and with diuresis Decreased in extensive renal disease

Urea Clearance

NORMAL RANGE Should amount to 75 to 125 per cent of normal (Standard 40 to 65 ml of blood cleared of urea per min)

TECHNICAL NOTES Serum and urine Two exactly timed 1 hour samples of urine are collected The urine flow should not be less than 1 5 ml /min

CLINICAL CLUES Increased in fever diuresis and after a protein meal Decreased in renal disease (with impaired filtration), oliguria, shock, and anemia

Inulin Clearance

NORMAL RANGE The inulin clearance in the "ideal" man (i e, having a body surface of 1 73 square meters) averages 125 ml of plasma cleared of inulin per minute with the normal range varying from 100 to 150 ml per minute *It is* necessary in an individual case to ascertain the body surface area (which can be obtained from the Dubois surface area tables that accompany basal metabolism equipment) The inulin clearance per square meter per minute is determined *after* which the clearance is calculated on the basis of 1 73 square meters

TECHNICAL NOTES This test is performed in the morning with the patient kept in the reclining position It is necessary to give one glass of water at 6 30 a m and every half hour thereafter until the test is completed in order to promote a free flow of urine A light breakfast is ingested at 7 30 a m (one-half glass of milk and one slice of buttered toast) At 8 a m 10 gm of inulin (dissolved in 100 ml of physiologic saline solution) is injected intravenously at a rate of 10 ml per minute The bladder is emptied in one hour and the urine discarded The urine is then collected in one and two hours, measured and analyzed for its content of inulin Thirty and ninety minutes after the initial emptying of the bladder, blood is collected into oxalate centrifuged and the plasma analyzed for inulin

The inulin clearance is determined from the formula $\frac{UV}{P}$ (where U equals the mg of inulin per 100 ml of urine, V equals the ml of urine per minute and P equals the mg of inulin per 100 ml of plasma)

CLINICAL CLUES This determination is a measure of glomerular filtration inasmuch as the polysaccharide inulin is excreted entirely through the glomeruli without being either excreted or reabsorbed by the renal tubules There is a general correlation between the urea clearance and the inulin clearance (While endogenous creatinine is chiefly excreted by the glomeruli, a small amount is also excreted by the renal tubules) These clearance studies are of some value in the study and management of certain patients with hypertension and acute or chronic renal disease

Para aminohippuric Acid (PAH) and Diodrast Clearance

NORMAL RANGE The following are the mean values for the effective renal plasma flow and tubular excretory mass

	MALES	FEMALES
Effective renal plasma flow (clearance of either substance in ml. per minute)	697 ± 135	594 ± 102
Maximal tubular excretory capacity (Tm_D mg iodine per minute)	51 8 ± 8 73	42 6 ± 9 46

TECHNICAL NOTES The technique involves the injection of a priming dose of the test substances followed by a sustaining infusion Only a single period for collecting urine is needed An inulin test is concurrently performed to measure the glomerular filtration rate The details of this test are omitted here but can be readily obtained (67b) PAH has largely supplanted the use of Diodrast inasmuch as it is less extensively bound to the plasma proteins its quantitative determination is simpler, and there is no penetration of the red cells

CLINICAL CLUES These substances are used in this manner to measure the renal blood flow and the tubular excretory mass (maximal tubular excretory function) When injected intravenously so as to produce low plasma concentrations, they are almost completely cleared from the plasma in one passage through the kidney (The excretion occurs chiefly by the tubules) The clearance value of either is therefore equivalent to the renal plasma flow The PAH clearance correlates generally with the 15-minute PSP test These studies may aid in the evaluation of acute and chronic renal disease and in the management of hypertension

Evaluation of Unilateral Renal Disease in Hypertension (73) (T-887b)

NORMAL RANGE The volume of urine and the concentration of sodium are either the same or proportionately comparable from each kidney This applies both to normal kidneys and when bilateral renal disease is present

TECHNICAL NOTES The urine from each ureter is simultaneously collected after previous hydration (200 ml water every 15 minutes for one hour preceding the test) The volumes and sodium concentrations are determined and compared Care must be taken to avoid bladder leakage and to insure an adequate urine flow The patient should have been on a regular salt diet for the previous 3 to 4 days The test is contraindicated in the presence of azotemia

CLINICAL CLUES In this study of *total* renal damage the finding of a concomitant unilateral reduction in both the urine output and the sodium concentration suggests the diagnosis of unilateral renal hypertension This test is also indicated in hypertensive patients without obvious renal disease who either exhibit severe or accelerated hypertension or whose response to antihypertensive medication is very poor It is considered positive if the urine volume is reduced by 60 per cent or more and if the sodium concentration is reduced by 16 per cent or more in the urine coming from one kidney as compared with that from the other Such observations may indicate further the beneficial effects to be derived from a nephrectomy

The radioactive Diodrast renogram in which external monitors measure the rates of accumulation and disappearance of I^{131} labeled Diodrast over the renal areas after an intravenous injection of the test material also holds much promise in the detection of unilateral renal disease (88)

KIDNEY BIOPSY

(See Section XI, p 794)

X-RAY STUDIES

KUB Film

TECHNICAL NOTES When technically satisfactory, this simple 'flat' or survey film is a most valuable procedure The kidneys, adrenals ureters bladder, prostate seminal vesicles lumbar spine, hips, pelvis, psoas muscles, and retroperitoneal fat lines are encompassed Numerous shadows can simulate renal calculi including fecaliths, material in the bowel, calcified lymph nodes, gallstones, phleboliths artifacts of all descriptions and calcification within the kidneys, spleen, or pancreas (79) *Care must be taken not to overlook small calculi that are lodged in the terminal portion of the ureter*

CLINICAL CLUES The presence of opaque calculi, metastatic disease to the local bones a perinephric abscess, and abnormalities in the size shape or position of the kidneys may be ascertained in this one film Up to 90 per cent of urinary tract calculi are opaque to x ray Calcification of the vas deferens suggests diabetes mellitus whereas *calcification of the seminal vesicles is apt to occur in tuberculosis* The presence of kidney shadows of normal size in the patient with acute urinary suppression and in the absence of ureteral obstruction is highly suggestive of a primary parenchymal insult

Intravenous Pyelography

NORMAL RANGE Films are taken at 5, 10 15, and 25 minutes following the intravenous infusion of Urokon (35 per cent or 50 per cent) or Hypaque If no filling is seen, the films are continued at 15 minute intervals for up to several hours Filling may be poor if the kidneys are unable to concentrate urine Compression is usually not needed

There are very few contraindications to this test if it is needed Intravenous pyelography should not be attempted in the patient with acute urinary suppression (T-180c) The test dose for sensitivity (cutaneous or ophthalmic) is occasionally misleading The contrast media is administered after giving 20 mg of Chlortrimeton intramuscularly particularly if an allergic background exists

Catharsis and an eight hour abstinence from fluids allow for better visualization of the retroperitoneal tissues and for better concentration of the contrast medium by the kidneys because of the mild dehydration In the presence of moderate uremia, however, intravenous urograms should be taken *without* prior dehydration of the patient (83a)

CLINICAL CLUES This study is very helpful in diagnosing unilateral renal disease in hypertension (T-886 887) renal tumors, retroperitoneal tumors (T-669) and adrenal tumors It also supplements the other renal function studies Even in the presence of overt pathologic changes affecting one kidney, *it is important always to search for disease of the other kidney or ureter* (T-1242-1245) Changes may be minimal when a renal tumor expands laterally

This procedure should be routine in all cases of prolonged and unexplained fever or anemia (T-372) It may also be helpful in detecting mass lesions in the body or tail of the pancreas (181) The presence of a nephrogram (i e the gradual increase in density resulting from the collection of the contrast material in the tubules) is indicative of an acute obstruction, usually less than four days duration Whereas congenital polycystic disease of the kidneys is invariably bilateral and progressive this is not necessarily the case in other types of multiple renal cysts

Retrograde Pyelography with Dyes or Air

TECHNICAL NOTES Following insertion of the catheter(s) under cystoscopic guidance up to or just below the renal pelvis the opaque medium is injected Too rapid distention often results in spasm and incomplete filling of the renal pelvis Overdistention should be guarded against particularly when flank pain is produced due to the confusing radiographic effects of pyelotubular backflow The presence of an air pocket in the pelvis should not be interpreted as a filling defect

Retrograde pyelograms should be recommended with the greatest of caution in the presence of severe chronic nephritis Furthermore because of the ever present danger of iatrogenic pyelonephritis retrograde pyelography should be withheld in cases of renal infection or minimal hematuria—particularly in children—with the diagnostic emphasis being focused on intravenous pyelography (even using double doses of the contrast media and compression techniques)

CLINICAL CLUES Retrograde studies are supplementary to intravenous pyelography A diagnosis of bladder disease should not be made solely on the basis *of intravenous pyelograms Necrotizing renal papillitis can be* suspected by various features including ulcerative or erosive papillary changes intramedullary sinus formation parenchymal cavitation, ureteral or calyceal obstruction and clublike papillary fossae (T–39a)

Nephrotomography

TECHNICAL NOTES After preliminary tomograms have been taken to determine the best level 70 *per cent* Urokon or Hypaque *is rapidly injected* A #12 Robb-Steinberg angiocardiographic needle is preferred Tomograms are taken at both the preselected level and at 1 cm above and below it timed by the Decholin end point and in 5 minutes

CLINICAL CLUES This technique may prove to be valuable in the preoperative diagnosis of benign single or multiple renal cysts and of malignant tumors Its advantages relate to the excellent delineation of functional renal parenchyma free of superimposed intestinal and gas shadows

Renal (Abdominal) Angiography (70 75, 87, 248, 275)

TECHNICAL NOTES This procedure carries a definite risk of either serious renal injury or paraplegia with the use of the presently available contrast media It is performed under pentothal anesthesia using a 6-inch 18-gauge needle introduced below the left twelfth rib (above the level of the celiac axis) The aorta is best visualized in the first-second film while maximum filling of the vessels occurs at three to four seconds The right renal vessel and its tributaries are apt to fill more satisfactorily than the left due in large measure to the direction of the needle insertion

Technical failure to fill one or both vessels might result in the misdiagnosis of a thrombosis of the major renal vessels It is important to obtain sequential films that demonstrate both a full arteriographic and a capillary (nephrographic) phase of the circulation This is especially true in the evaluation of a kidney mass since the presence of irregularly branched tortuous small vessels of varying caliber are usually associated with a primary renal malignancy The hazards of abdominal *aortography will receive further comment in Section IX* (p 783)

CLINICAL CLUES This technique may be helpful in the preoperative differentiation of renal cysts renal tumors abnormalities of development retroperitoneal tumors and disorders affecting the renal arteries Tumors are usually

much more vascular than cysts As indicated, their neoplastic nature is further suggested by the presence of many abnormal tiny, intertwining vessels within the mass Aortography may be misleading in urologic diagnosis because of a number of factors, including (1) thrombosis or compression of the vessel leading to a malignancy, (2) misinterpretation of unusual lobulations of the kidney, and (3) inability to detect renal tumors measuring less than 2 to 3 cm in diameter (75)

Agenesis of the kidney, horse-shoe kidney, and an ectopic kidney can be detected rather readily by translumbar aortography The failure to visualize the polycystic kidney in serial films during this procedure is usually indicative of renal insufficiency (248b) It can also supply valuable information about a nonfunctioning kidney, particularly when intravenous pyelography reveals no contrast and when retrograde pyelography is unsuccessful

Translumbar aortography has been rather disappointing as a definitive diagnostic method in most abdominal and retroperitoneal diseases, with the possible exception of tumors in the lower retroperitoneum (248b)

Retroperitoneal Pneumography (see Section XII, p 803)

SECTION IV

Liver Function Tests and Other Related Studies [90, 91 94 96 100]

Ammonia (T-350 355)

NORMAL RANGE 40 to 70 microgm per 100 ml

TECHNICAL NOTES Plasma Special processing is needed More accurate and specific methods for estimating ammonia are necessary since there is an immediate liberation of this compound in shed blood Also, the present procedure is laborious and tricky particularly in the hands of those who are not familiar with microtitration techniques

CLINICAL CLUES Elevated in the exogenous' and chronic groups of ammonia intoxication that occur in severe liver disease and coma particularly when ammonium chloride therapy a high protein diet Diamox, ammonium resins or methionine are administered (These seem to respond more readily to L-glutamic acid than the spontaneous encephalopathy p 97)(93) Inasmuch as there is no elevation in uremia the blood ammonia content may serve as a useful basis of differentiating this entity from hepatic coma Arterial ammonia levels apparently correlate better with hepatic coma than the peripheral venous levels

Bile in Urine

NORMAL RANGE 0

TECHNICAL NOTES The foam test is sensitive, but it may be inaccurate if the patient is receiving penicillin streptomycin PSP riboflavin or atabrine The Ictotest (bilazo) the Harrison spot test (barium impregnated strip) and the Franklin test (Fouchet s reagent) can all be conveniently performed now

CLINICAL CLUES Bilirubinuria is an extremely sensitive indicator of liver dysfunction or biliary obstruction

Bilirubin (van den Bergh Test)

NORMAL RANGE Direct' 0 1 to 0 4 mg per cent Total 0 7 to 1 0 mg per cent (Indirect is the total minus the direct)

TECHNICAL NOTES It is the insolubility of the indirect form and *not* the nature of the protein binding which determines its failure to react in the diazo reaction without the addition of alcohol *Indirect-acting bilirubin is now known to* represent bilirubin that is not conjugated with glucuronic acid and because of its insolubility in water requires the addition of alcohol to initiate diazo coupling (T-

319) On the other hand, direct-reacting bilirubin is now regarded as being "combined"—rather than "free," as was previously considered—in that this pigment is conjugated with glucuronic acid (usually two molecules) by the liver to form an extremely water soluble compound

Bilirubin determinations can be performed on very small quantities of blood taken from heel punctures in infants suspected of having erythroblastosis (T-704a)

CLINICAL CLUES "Indirect" more elevated in hemolytic jaundice and constitutional hyperbilirubinemia "Direct" more elevated in obstructive jaundice, parenchymal jaundice and "chronic idiopathic jaundice with unidentified pigment in liver cells"

Constitutional hyperbilirubinemia and the syndrome of chronic idiopathic jaundice with unidentified pigment in liver cells are both important to recognize (T-333 334) They may be suspected if the other studies are relatively normal in the presence of a chronic mild icterus (pp 90 and 91)

An elevated indirect serum bilirubin alone does not usually occur within the initial weeks of a viral hepatitis The persistence of hyperbilirubinemia in the absence of other evidences of activity in posthepatitis patients is usually benign and should not be the sole basis for unduly prolonged treatment or restriction (97)

Biopsy of Liver (T-323)

TECHNICAL NOTES The intercostal approach is preferred by this author Biopsied tissue should be processed with additional stains for fat iron, and connective tissue Cultures are also taken where indicated The repeated performance of needle liver biopsies in the presence of an unrelieved biliary obstruction invites the possibilities of bile peritonitis and biliary fistulae

Previous scanning of the liver with a directional scintillation detector 24 hours following the intravenous injection of radioiodine-tagged human serum albumin will probably be found to increase the positive yield of needle biopsy specimens in cases of suspected metastatic cancer or the granulomatous diseases (92)

CLINICAL CLUES May be diagnostic of primary liver disease, lymphoma metastases hemochromatosis the granulomata hematogenous tuberculosis schistosomiasis sarcoidosis histoplasmosis, and brucellosis The presence of pigment in the liver cells and the associated absence of an inflammatory reaction in the syndrome of "chronic idiopathic jaundice with unidentified pigment in liver cells" should not be confused with bile stasis and obstructive jaundice (T-334)

Bromsulphalein (BSP) Test

NORMAL RANGE Less than 5 per cent retention in the serum after 45 minutes

TECHNICAL NOTES Serum 5 mg per kg of the dye should be injected intravenously and a 45-minute specimen drawn from the other arm The test is inaccurate if gross icterus is present, or if it is performed shortly after dye is ingested for visualization of the gallbladder

CLINICAL CLUES Elevated in extensive hepatic disease hepatitis acute yellow atrophy, cirrhosis, and neoplasm (may be an early sign) It is perhaps the best screening test for hepatitis "carriers" ("Many liver function tests are normal in carriers")(95)

This test has proved very valuable in evaluating the cause of massive upper gastrointestinal bleeding when varices due to cirrhosis are suspected (Shock, age fever and severe bleeding usually do *not* significantly increase bromsulphalein retention) (T-1351) When the BSP test is so used to diagnose possible underlying liver

disease as a cause of gastrointestinal hemorrhage however one must be aware of the fact that the anoxia resulting from massive blood loss *per se* can cause abnormal retention in the presence of a normal liver

A striking elevation of BSP retention in the absence of jaundice occurs early in the Budd Chiari syndrome (p 99) (T-361)

Cephalin Cholesterol Flocculation Test

NORMAL RANGE Up to ++ in 48 hours

TECHNICAL NOTES Serum Numerous sources for possible technical errors exist in this test

CLINICAL CLUES Readings of up to ++++ occur early in the course of extensive hepatic disease The results may be normal in the presence of liver damage if hypogammaglobulinemia is present

Hippuric Acid Test

NORMAL RANGE *Oral* 3 0 to 3 5 gm benzoic acid are excreted in 4 hours *Intravenous* 0 7 to 1 8 gm benzoic acid are excreted in 1 hour

TECHNICAL NOTES *Oral* 6 gm sodium benzoate are injected *Intravenous* the contents of a 20 ml ampoule (containing 1 77 gm sodium benzoate) are injected intravenously over 8 minutes

CLINICAL CLUES Reduced excretion occurs in extensive hepatic disease renal insufficiency and dehydration

Icterus Index

NORMAL RANGE 1 to 5 acetone 3 to 10 water

TECHNICAL NOTES Serum Less reliable than the bilirubin determinations

CLINICAL CLUES Elevated in jaundice and carotenemia

Rectum-to-Lung Ether Time Test ("Portal Circulation Time") (98)

NORMAL RANGE 14 to 58 seconds (mean 37 seconds)

TECHNICAL NOTES 3 ml of anesthetic ether are vaporized by hot water to a volume of 200 ml and injected rapidly into a rectal tube inserted 10 inches above the anus The time required for the first appearance of ether in the breath (either by the observer or by the patient) is noted

CLINICAL CLUES This test unfortunately has little diagnostic significance due to the wide overlapping variations both normally and in disease It is suggestive of altered portal circulation only when it exceeds 60 seconds It may be useful as a simple method for determining the patency of a portacaval or splenorenal anastomosis

Thymol Turbidity and Flocculation

NORMAL RANGE 0 to 4 units

TECHNICAL NOTES A thymol barbiturate buffer is added to the serum It has several advantages over the cephalin-cholesterol test in that it depends upon easily prepared stable solutions and can be completed within 30 minutes

In the thymol flocculation test the degree of flocculation is noted after 18 hours the range being expressed as 1+ to 4+ Flocculations greater than 1+ are generally abnormal

Clinical Clues This test is a very sensitive indicator of acute liver damage It is particularly valuable in the later stages of hepatitis In the absence of overt liver disease, the thymol reactions are more sensitive indicators of elevations in the serum globulin than are the cephalin cholesterol flocculation tests

The routine use of the thymol turbidity test has been advocated as a practical method of screening unsuspected hepatitis in blood donors, using the level of 8 units or above as the criterion for rejection

Tyrosinuria

Normal Range 0

Technical Notes Careful examination of the urine sediment (Also see Section III)

Clinical Clues May be massive in acute yellow atrophy It is occasionally also noted in obstructive jaundice and in hepatitis

Urobilinogen

URINE

Normal Range 0 to 4 mg per diem

Technical Notes Inaccurate if the patient is receiving (oral) broad spectrum antibiotics Carefully prepared Ehrlich s reagent and pure hydrochloric acid must be used A 2-hour specimen (1 to 3 p m) is examined

Clinical Clues Valuable in both the diagnosis and observation of jaundice liver and biliary tract disease and the hemolytic anemias Urinary urobilinogen may be present in obstructive jaundice if a cholangitis is present *above* the obstruction Porphyria should be suspected if an unexplained elevated urinary urobilinogen test is present Absent in obstructive jaundice and in cholangiolitic hepatitis

FECES

Normal Range 40 to 280 mg per diem

Technical Notes Collection of the entire stools (preferably over a period of several days) is necessary Not reliable if the patient is on sulfonamides or antibiotic therapy

The method of Watson measures the breakdown products of bilirubin in the stool Grossly acholic stools can contain from 10 to 15 mg per day (A gray stool is not necessarily acholic)

(To collect the specimen a sheet of Saran Wrap is placed beneath the toilet seat or over the bed pan allowing ample slack)(377)

Clinical Clues Greatly increased in hemolytic jaundice (600 to 2000 mg per day) When a marked anemia exists slightly elevated levels are highly significant In hepatitis the fecal urobilinogen may be increased slightly or not at all in contrast to the considerable increase in the urinary urobilinogen Very low levels (less than 5 mg daily) are characteristic of complete biliary obstruction particularly in the case of neoplasms A rise in suspected calculous disease may portend relief of the obstruction

Zinc Sulfate Turbidity Test (99)

Normal Range 4 to 12 units

Technical Notes Serum

CLINICAL CLUES The ZST test is a rapid and useful qualitative procedure for the determination of serum gamma globulin It is not affected by the levels of serum albumin Its greatest value is in the diagnosis of chronic hepatitis and cirrhosis particularly when the problem relates to long standing jaundice It is not specific for liver disease however since elevations also occur in those disorders associated with rises in the gamma globulin

Obstructive jaundice must be considered when the result is found to be normal in the presence of long standing jaundice Low ZST values are most frequently encountered in severe renal disease with proteinuria malignant hypertension and metastatic carcinoma

Related Studies of Liver Function Tests Presented Elsewhere

Blood nonprotein nitrogen and urea (Section III)
Congo red test (Section II)
Serum cholesterol cholesterol esters and lipids (Section II)
Serum iron (Section II)
Phosphatase alkaline (Section II)
Serum proteins (Section II)
Prothrombin time *(Section I)*
Blood sugar (Section II)
Glucose tolerance test with serum inorganic phosphorus and potassium (Sections II and V)
Serum transaminase (Section II)
Cholinesterase (Section II)
Esophagoscopy (Section VII)
Infra red photography (Section XI)
Abdominal aortography (portal venography) (Section VII)
Vitamin K trial (Section XIII)
Corticotropin trial (Section XIII)

SECTION V

Studies of Endocrine Function

ANTERIOR PITUITARY
(pp 30 to 34)

Follicle-Stimulating Hormone (FSH)

NORMAL RANGE Before puberty less than 6 5 mouse units After puberty 6 5 to 52 mouse units After the menopause 100 mouse units

TECHNICAL NOTES 24 hour urine specimen Proper collection and transportation are very important

CLINICAL CLUES Increased in primary gonadal failure of either the testes or ovaries Its absence in postmenopausal women, or in premenopausal women with hypothyroidism and amenorrhea is indicative of Simmond s disease (T-101 102) *Very low values of the FSH have been encountered in primary myxedema* when severe liver disease was also present (T-37)

Insulin Tolerance Test (115, 116)

NORMAL RANGE The glucose level decreases to half of the fasting level in 20 to 30 minutes and should return to the fasting level in 90 to 120 minutes

TECHNICAL NOTES 0 1 unit insulin per kg is injected intravenously The patient should be observed carefully if an increased sensitivity to hypoglycemia is suspected

CLINICAL CLUES *Insulin resistance* (delayed or absent fall) occurs in Cushing s syndrome and hyperpituitarism *Hypoglycemic unresponsiveness* (delayed or absent terminal rise) occurs in Addison s disease hypopituitarism and hyperinsulinism The development of recent sensitivity to insulin in a diabetic suggests a complicating hypopituitarism or adrenocortical insufficiency

Serum Cholesterol

NORMAL RANGE See Blood Chemistries (p 688)
CLINICAL CLUES Usually normal in pituitary myxedema

Thyroid Stimulating Hormone

NORMAL RANGE See Thyroid ' below

CLINICAL CLUES This determination may help in distinguishing primary and pituitary myxedema (T-6-8 27)

Serum Phosphorus

NORMAL RANGE See Blood Chemistries (p 691)

CLINICAL CLUES Values above 5 mg per cent are suggestive of excessive growth hormone secretion It may also serve as a valuable guide in gauging the amount of therapeutic x radiation delivered to the pituitary (T-98)

X Rays of the Sella Turcica (121)

NORMAL RANGE A depth of 10 mm and an anteroposterior measurement of 12 to 15 mm are generally considered to be the upper limits of normal An area exceeding 130 sq mm is considered enlarged (82)

TECHNICAL NOTES The sella in routine skull films is measured with a special sella meter The configuration of the sella the presence of destruction of the clinoids and any suprasellar calcification should also be observed

CLINICAL CLUES This structure should be studied in problem cases of hypertension thyrotoxicosis diabetes mellitus arthritis amenorrhea, and impotence An extrasellar tumor should be suspected if destruction of the anterior clinoids is seen

Visual Field Studies (see Section XIII, p 809)

Determination of Bone Age (110)

NORMAL RANGE The appearance of the secondary ossification centers and their time of fusion are noted There are many normal variations Allowances of 6 months 1 year and 2 years either way from the figures cited in the various charts should be made in children 5 years, 10 years and 15 years respectively In general girls run about 1 year ahead of boys between the ages of 5 and 12 after 14 the difference is about 2 years

TECHNICAL NOTES *Areas best taken for bone age studies*

One to five Full figure (divided on two films) hands and feet lateral knee for patella

Six Hands and wrist foot elbow shoulder

Seven Pelvis hand and wrist foot

Eight to ten Elbow foot hand and wrist

Eleven to twelve Elbow hand and wrist

Thirteen Hip with half pelvis elbow hand and wrist foot

Fourteen to fifteen Scapula pelvis foot hand elbow

Sixteen to seventeen Pelvis

Eighteen Hand and wrist, foot pelvis with hip joint ankle clavicle (sternal end)

Nineteen to twenty Hand and wrist, knees ankle

Twenty two to twenty five Clavicle (sternal end) pelvis, knee

CLINICAL CLUES A marked delay in the appearance of the various centers and closure of the epiphyseal lines occurs in hypothyroidism, and in gonadal and anterior pituitary deficiency Advanced development and early union of the epiphyses is noted in overactivity of the pituitary and thyroid glands

POSTERIOR PITUITARY

(pp 33 to 34)

Withdrawal of Fluids (T-104, 105)

TECHNICAL NOTES The urine volume and specific gravity should be fol

lowed The patient should be observed very cautiously over 8 to 12 hours during the day

CLINICAL CLUES Aids in differentiating true diabetes insipidus from functional polydipsia (the specific gravity rising only in the latter), but not from chronic nephritis In true diabetes insipidus the *specific gravity of the urine* rarely exceeds 1 005 and the daily urine volume is usually greater than 4 liters, even with the temporary withholding of liquids

Hypertonic Saline Test (Hickey-Hare Test) (111, 124)

TECHNICAL NOTES Following an infusion of 5 per cent glucose, 3 per cent saline is infused intravenously (30 drops a minute) The volume in three 15-minute collections of urine on dextrose should be compared with four 15 minute collections on saline

CLINICAL CLUES In individuals with normal function of the supraoptico hypophyseal tract a fall in urine flow occurs with the saline infusion due to the release of antidiuretic hormone In diabetes insipidus, a rise occurs (This test helps to differentiate psychogenic polydipsia from true diabetes insipidus)

Pitressin Test (145)

TECHNICAL NOTES 0 1 ml of Pitressin is given intravenously It may be given in conjunction with the hypertonic saline test

CLINICAL CLUES The diuresis is inhibited in true diabetes insipidus (This test helps to differentiate the latter from primary renal disease)

Nicotine Test (134)

TECHNICAL NOTES The patient smokes 1 to 3 cigarettes rapidly and deeply

CLINICAL CLUES *An immediate antidiuresis occurs normally, but not in* diabetes insipidus This study is particularly useful when the hypertonic saline-Pitressin test is contraindicated

Determination of Osmotic Pressure of Blood and Urine

TECHNICAL NOTES The osmotic pressure of a heparinized blood sample and urine are determined after a 3 hour period of abstinence from water and food The osmotic pressure is determined from the depression of the freezing point The total solute concentration is expressed in milliosmols per liter

The term milliosmols has been utilized to express the osmotic relationships between extracellular and intracellular fluid It refers to particles of a substance with one milliosmol being 1 1000 of the atomic weight When the valence of a substance is one its milliosmol value is one when the valence is two, the milliosmol value is one-half The sum of the milliosmols of the cations and anions represents the total osmolar tonicity and is normally 310 milliosmols for the extracellular fluid It is primarily related to the concentrations of sodium in the plasma and interstitial spaces which in turn are regulated by many factors, including aldo sterone secretion and the osmoreceptors

CLINICAL CLUES *In diabetes insipidus the total solute concentration* of the urine is always less than that of the blood in the uncontrolled patient It can usually be reversed following the administration of Pitressin A greater total solute *U/P ratio is always found* in such cases than in water loaded individuals with diabetes mellitus chronic nephritis the Kimmelstiel Wilson syndrome and normal subjects

THYROID
(pp 16 to 19)

Iodine (Protein Bound or Hormonal) (105, 106, 113)

NORMAL RANGE 3 5 to 8 0 microgm per cent

TECHNICAL NOTES Serum False elevations may be produced by iodide therapy, x ray contrast media iodine on the skin, iodine-containing suppositories, thyroid extract pregnancy, and estrogens The test is long and subject to many technical errors

Diodrast and Urokon are usually eliminated within four weeks in contrast to Lipiodol, Pantopaque and the gallbladder contrast media (due to either the prolonged deposition of the dye or to the enterohepatic recirculation) Protein bound iodine testing should therefore be delayed for the following approximate periods because of the probable resulting contamination with iodide

Mercurial diuretics	three days
Retrograde pyelography Schiller s test Floraquin, Wyanoids, Diodoquin, Lugol s solution KI and expectorants or vitamin preparations containing iodides or kelp	three weeks
Thyroid replacement or antithyroid medication containing iodides	one month
Intravenous pyelography	two months
Bronchography salpingography or gallbladder series	four months
Myelography	nine months

CLINICAL CLUES Elevated in hyperthyroidism and hyperpituitarism Decreased in hypothyroidism hypopituitarism, and by the administration of ACTH, cortisone the mercurials and the antithyroid drugs In practice the greatest value of this test is in the diagnosis of hyperthyroidism when the value exceeds 10 microgm per 100 ml

Basal Metabolic Rate (127)

NORMAL RANGE −20 per cent to +20 per cent (Note this wide range of normal)

TECHNICAL NOTES Numerous potential technical errors exist both in the apparatus and in the preparation of the patient When accurately performed how ever, the results may be very reliable and significant Smoking must be stopped for one day prior to the test Determination under pentothal anesthesia has occasion ally proved helpful (104)

CLINICAL CLUES Hypometabolism is *not* synonymous with hypothyroid ism Extrathyroidal causes of hypermetabolism include pheochromocytoma acromegaly, anemia leukemia congestive heart failure Paget s disease fever caffeine polycythemia and neurosis (T–46) A normal test result does *not* exclude hyper thyroidism Decreased in starvation hypothyroidism, hypopituitarism edema and following prolonged periods of rest

I^{131} Studies (105, 106)

RATE OF RADIOIODINE ACCUMULATION BY THE THYROID GLAND

NORMAL RANGE 10 to 40 per cent uptake in 24 hours (This measures the rate of activity of the thyroid gland rather than the degree of stimulation of the body cells by thyroid hormone)

TECHNICAL NOTES A tracer dose of 10 to 30 microcuries is ingested There are many potential technical errors, particularly from iodine in the various diagnostic dyes and medications (including many vitamin mineral preparations) (128) thyroid cortisone Butazolidin, cobalt, and PAS Two possibly misleading situations in which excessive uptakes of radioactive iodine may be encountered consist of (1) the colloid goiter due to a relative or absolute lack of iodide, and (2) the cessation of antithyroid medication with a resulting high 'rebound"

The taking of counts at 2 6, and 24 hours is advocated by certain clinicians as a means of separating individuals with high initial uptakes and rapid turnover rates from patients with thyrotoxicosis (who continue to show a rise in uptake at 24 hours) The former situation may occur when there has been a subtotal thyroidectomy, and is characterized by the flattening of the curve at 6 hours

CLINICAL CLUES The hyperthyroid range is 50 to 100 per cent (Values between 35 and 55 per cent are equivocal) Less than 10 per cent is suggestive of hypothyroidism Factitious hyperthyroidism should be suspected if little uptake is noted in the presence of hyperthyroid features (T-45) A greater uptake has been observed in the apparently euthyroid relatives of patients with Graves disease (T-1225)

Patients with clinical hypopituitarism (in contrast to hypophysectomy) may have appreciable I^{131} uptakes by their thyroids ranging from 10 to 25 per cent (T-106c) While a few malignancies of the thyroid will show an uptake of I^{131}, the presence of a functioning nodule is usually presumptive evidence that the nodule is benign

Although the blood iodine may remain elevated for very long periods of time after the ingestion of certain gallbladder dyes the I^{131} uptake is no longer affected after a few weeks The interval is actually shorter in hyperthyroid patients due to the faster turnover of iodide

I^{131} EXCRETION IN TWENTY FOUR HOURS I^{131} CLEARANCE I^{131} CONVERSION RATIO I^{131} UPTAKE AFTER THYROID OR TRIIODOTHYRONINE

TECHNICAL NOTES All these studies are useful in the hands of experienced investigators, but are liable to many sources of technical error and clinical misinterpretation

THYROID STIMULATING HORMONE (TSH) TEST (102)

NORMAL RANGE A significant increase in the I^{131} uptake after the hormone is given normally occurs A determination 3 to 6 hours after the TSH has been found to be reliable in most instances

TECHNICAL NOTES The I^{131} uptake is determined before and after administration of the hormone 10 to 25 mg of TSH are given intramuscularly every 8 hours for 2 days particularly when attempting to differentiate primary and secondary hypothyroidism More recently a single injection of 4 units is being advocated (141)

CLINICAL CLUES No increased uptake occurs in primary hypothyroidism, but it may become increased in pituitary myxedema This test is most useful in differentiating (1) the euthyroid patient who is taking dessicated thyroid from the hypothyroid patient taking this medication and (2) the patient with struma lymphomatosa from the one with a nontoxic adenomatous goiter

Biopsy of the Thyroid Gland (see Section XI, p 801)

Therapeutic Diagnostic Tests (see Section XIV, p 812)

Withdrawal Tests (see Section XV, p 818)

PARATHYROIDS (103) (T–69, 70)
(pp 23 to 28)

Serum Calcium

NORMAL RANGE 9 5 to 10 5 mg per cent (4 5 to 5 5 mEq per liter) (higher in children)

TECHNICAL NOTES Serum A serum protein determination should accompany this test to indicate the relative proportions of bound and ionizable calcium

CLINICAL CLUES Elevated in parathyroid overactivity vitamin D excess excessive androgen and estrogen therapy, and extensive metastases Also elevated in sarcoidosis and myeloma due in large measure to the elevated serum protein If elevated in the presence of an insulinoma, one should look for multiple endocrine adenomata Hypercalcemia without hypercalciuria or hyperphosphatemia occurs in the milk alkali syndrome (Burnett) (p 406)

Decreased in renal insufficiency, the postparathyroidectomy state osteomalacia, diarrhea acute pancreatitis steatorrhea and hyperthyroidism

Urinary Calcium (103)

SULKOWITCH TEST

NORMAL RANGE *1 plus or less*

TECHNICAL NOTES The patient should be kept on a diet free of milk products for 3 days Collect in a special bottle with hydrochloric acid

The urine must not be too dilute Coccal pyelonephritis may be responsible for calciuria in the presence of hypocalcemia

CLINICAL CLUES Increased in hyperparathyroidism diuresis acidosis and with an excess of vitamin D androgens or estrogens Decreased in hypoparathyroidism, hypothyroidism renal insufficiency steatorrhea diarrhea and vitamin D deficiency

It is important to bear in mind the relatively common occurrence of hypocalcemic hypercalciuria during therapy with vitamin D and dihydrotachysterol in the management of hypoparathyroidism a phenomenon that tends to refute the reliability of the Sulkowitch test as a guide to such therapy (T–82b)

QUANTITATIVE

NORMAL RANGE Less than 150 mg per diem

TECHNICAL NOTES See Sulkowitch Test above

Blood Phosphorus (T–69, 70)

NORMAL RANGE 3 0 to 4 5 mg per cent (infants up to 6 0 mg per cent)

TECHNICAL NOTES Serum Must be drawn in the fasting state

CLINICAL CLUES *Decreased in primary hyperparathyroidism It may be* increased however when renal insufficiency is also present Increased in hypoparathyroidism pseudohypoparathyroidism and hypervitaminosis D

Ellsworth Howard Test (T-83 85)

NORMAL RANGE A moderate rise in urinary phosphates occurs, usually twofold or more

TECHNICAL NOTES 200 U S P units (2 ml) of parathyroid extract are administered to the fasting patient, preferably in the afternoon or early evening (to coincide with the diurnal variation in urinary phosphorus output) Hourly urine specimens for 3 hours before the injection and for 3 to 5 hours afterwards are analyzed for their phosphorus content

CLINICAL CLUES An inability to respond to parathyroid hormone with *increased urinary phosphates occurs in the "target-organ defect" of pseudohypo*parathyroidism If the phosphates are increased, a diagnosis of true hypoparathyroidism can usually be made It must be appreciated that (1) an increase in the excretion of urinary phosphorus should not be attributed to the administration of parathyroid extract unless the normal diurnal rise in urinary phosphorus has been taken into account and (2) variations in the extract rather than an abnormal renal response may account for the failure of phosphorus excretion to change

Response to Intravenous Calcium (125)

NORMAL RANGE In normal subjects, there is a rise in serum phosphorus and a fall in urine phosphorus after the calcium infusion

TECHNICAL NOTES *The 24 hour phosphorus excretion on the day of the* calcium infusion (totaling 1 0 gm over a period of several hours) is compared with those on the preceding and following control days

CLINICAL CLUES In patients with hypoparathyroidism, the 24 hour urinary phosphorus excretion rises after the calcium infusion The intravenous calcium test is of little value in distinguishing between hyperparathyroidism and other causes of hypercalcemia Its greatest value may be in diagnosing a parathyroid adenoma in the normocalcemic patient

Phosphorus Deprivation Test (see Section XV, p 819)

OVARIES—PLACENTA

(pp 34 to 37)

Chorionic Gonadotropin (A-Z Test)

NORMAL RANGE Negative

TECHNICAL NOTES Serum or urine

CLINICAL CLUES Positive in pregnancy, hydatid mole and chorionepithelioma

Follicle-Stimulating Hormone (FSH)

NORMAL RANGE See Anterior Pituitary (p 720)

CLINICAL CLUES Increased in primary ovarian agenesis and insufficiency Decreased in secondary ovarian insufficiency (hypothalamic or anterior pituitary disorders)

Vaginal Smear (140)

NORMAL RANGE The presence and appearance of the epithelial and white

blood cells vary during the several phases of ovarian activity with their concomitant uterine changes (proliferation, secretion) (Also see Exfoliative Cytology p 790)

Technical Notes Cells are obtained by either a swab or by the aspiration of material from the posterior fornix These should be promptly studied or immediately fixed in ether 95 per cent alcohol Various stains may be applied The examination is of little value in the presence of vaginitis and other inflammatory conditions It may be necessary to review a series of smears over a period of at least 10 days in the middle of the cycle in order to determine with certainty when the production of progesterone starts

Clinical Clues This study may be of great value in evaluating the occurrence of ovulation or its absence in cases of sterility and amenorrhea Marked estrogen deficiency is characterized by the presence of round ovoid basophilic cells with hyperchromatic nuclei numerous leukocytes and some mucus As estrogen deficiency is corrected the cells are derived from the more superficial layers, the nuclei become vesicular, and the leukocytes diminish in number A castrate vaginal smear in the presence of multiple congenital defects suggests the Turner syndrome Biologically detectable estrogens can still be found in the urine of women who have an atrophic endometrium

Endometrial Biopsy

Normal Range In the estrogen proliferative phase the endometrium contains straight tubular glands lined by columnar cells with a basal nucleus In the progesterone-secretory phase the glands become markedly convoluted and the lining cells are filled with glycogen containing vacuoles (Also see Section XI p 794)

Technical Notes This test could be performed as an office procedure It is best done within 24 hours after the onset of the menses since at such a time it is generally painless and yields the most information to the trained pathologist

Clinical Clues This study permits evaluation of the secretion of both ovarian hormones It is also of value in proving that ovulation has occurred in demonstrating total ovarian failure and in the diagnosis of glandular and cystic hyperplasia

Pregnanediol (Urinary) (142)

Normal Range 5 to 20 mg per diem during a normal corpus luteum phase 40 to 50 mg per diem in pregnancy

Technical Notes A 24-hour specimen may be required in nongravid patients Various modifications of the Venning or Sommerville methods are employed

Clinical Clues This substance appears in the urine following ovulation and while the corpus luteum is active Most reports have shown it to be an unreliable test in the diagnosis of either pregnancy or threatened abortion It is of some value in the diagnosis of anovulatory bleeding

Culdoscopy and Culdotomy (T–125)

Technical Notes Inspection is performed with the Becker culdoscope or the Doyle pelviscope in the knee-chest and lithotomy positions respectively It is particularly advantageous in the presence of marked obesity, where palpation of the ovaries may be unsatisfactory Few complications have been reported in experienced hands It can even be performed through the virginal introitus

CLINICAL CLUES May be diagnostic of endometriosis unruptured tubal pregnancy pelvic inflammatory disease, and sterility problems The ovaries present characteristic appearances in the Stein Leventhal syndrome, hyperthecosis, ar rhenoblastomas, and the rare hilar cell tumors If they appear normal in the presence of amenorrhea, hirsutism and obesity adrenal disease should be suspected

Basal Temperature Graphs (143, 146)

NORMAL RANGE About the time of ovulation, there is a brief fall, which is followed in turn by a rise in the basal temperature of from 0 6 to 1 0 degree F It then remains elevated until the onset of menstruation, at which time it drops

TECHNICAL NOTES Basal body temperatures are taken at the same time each morning on awakening by means of a rectal thermometer inserted for five minutes The Cornell ovulation thermometer is particularly suited for such readings

CLINICAL CLUES When the observations are clear cut this test may be of help in problems of fertility since it establishes the time and occurrence of ovulation It can aid in timing endometrial biopsies, intercourse, and artificial insemination The persistence of a postovulatory rise in the basal temperature indicates the probable presence of a functioning corpus luteum

Sex Chromosome Study (119, 314)

NORMAL RANGE A distinct mass of deeply stained chromatin is found peripherally, primarily in the nucleus of cells from female donors

TECHNICAL NOTES Smears from the oral mucosa are obtained by scraping the inner surface of the cheek with a tongue depressor and spreading the material onto glass slides The slides are then fixed in 50-50 alcohol-ether, gradually hydrated stained with 1 per cent cresyl violet solution, differentiated in 95 per cent alcohol and dehydrated in dehydrated alcohol The use of pinacyanole as the stain has both simplified the technique and enhanced the accuracy of oral mucosal and blood smears for the study of chromosomal sex (119b)

CLINICAL CLUES This test obviates the skin biopsy for the determination of genetic sex It may prove of considerable aid in evaluating and advising patients with pseudohermaphroditism and gonadal dysgenesis (T-125 128) The small chromatin body that is visualized on the inner surface of the nuclear membrane is very infrequently found in genetically male cells (in which case it is less prominent and smaller) It represents a desoxypentosenucleic acid component of the paired X chromosomes of the female that remains as such a nuclear organelle in between mitoses

While it is now possible to identify accurately the sex of the baby before delivery from a study of the desquamated fetal epithelial cells within the amniotic fluid, the potential hazards to the fetus by amniotic puncture are apt to be very serious (119c)

The Carbon Dioxide Insufflation Test (Rubin)

NORMAL RANGE If the tubes are patent the pressure will rise to 100 mm of mercury and then fall fluctuating between 40 and 60 mm of mercury Referred shoulder pain is indicative of the entrance of the gas into the peritoneal cavity

TECHNICAL NOTES A measured amount of carbon dioxide is introduced into the cervix with the gas pressure being measured by a standard manometer At least 100 ml of the gas must be given to produce the shoulder pain The test is

best performed at the midcycle Carbon dioxide is much more comfortable and safer than oxygen (which not only may cause air embolism but also supports combustion) (242)

This test must not be performed when there has been recent infection or active bleeding inasmuch as endometriosis might be disseminated in the latter instance When the possibility of a functional blockage of the tubes exists the test should be repeated with sedation several days later during the secretory phase of the cycle

Suction endometrial biopsy can be combined with both uterotubal insufflation and hysterography by means of a modified insufflation cannula (148b) There are many obvious economic and time-saving advantages to performing these three diagnostic procedures one after the other

CLINICAL CLUES While this study does not test ovarian function it is one of the most valuable procedures in the evaluation of sterility If tubal impatency is present there will be no referred shoulder pain Furthermore the pressure will rise to 200 mm of mercury and not fall Tuboplasty with the current surgical techniques has been followed by pregnancy in one fifth of these patients especially when the obstruction followed a previous tubal ligation

TESTES

Urinary 17 Ketosteroids

NORMAL RANGE See Adrenal Cortex below

CLINICAL CLUES A useful index of Leydig cell function which accounts for one third of the total urinary 17 ketosteroids in males Increased in certain testicular tumors

Spermatozoa in the Semen (136, 147)

NORMAL RANGE 3 to 5 ml volume 60 to 120 million per ml with 60 to 80 per cent exhibiting normal motility At least 85 per cent should be of normal size and shape

TECHNICAL NOTES The specimen must be collected in a clean glass container and examined within 3 hours after ejaculation

CLINICAL CLUES Very valuable in the evaluation of postpubertal hypogonadism and in infertility problems

Follicle Stimulating Hormone (FSH)

NORMAL RANGE See Anterior Pituitary' above

CLINICAL CLUES Increased in the Klinefelter syndrome and in primary gonadal disease Decreased in gonadotropic insufficiency

Biopsy (102, 126, 138)

TECHNICAL NOTES May be readily performed under local anesthesia

CLINICAL CLUES Very helpful in ascertaining the presence or cause of disorders and tumors affecting the seminiferous tubules and the interstitial (Leydig) cells

The Postcoital Test

NORMAL RANGE The presence of normal spermatozoa indicates their production by the male their ability to reach the cervix in adequate numbers and their receptivity by the cervix

TECHNICAL NOTES Intercourse is carried out within one hour prior to the examination after four days of abstinence and a douche the preceding evening

CLINICAL CLUES This study is regarded by many students of infertility as the most necessary test after tubal insufflation and semen analysis (148a) A negative or poor result might indicate that there are no spermatozoa being produced, errors in coital technique, death of the spermatozoa, or a hostile cervix

PANCREAS

(pp 19 and 69)

Blood Sugar and Urine Sugar (T–255, 256)

NORMAL RANGE See "Blood Chemistries' and ' Kidney Function Urinalysis," (pp 687 and 704)

CLINICAL CLUES A fasting blood level of less than 50 mg per cent suggests hyperinsulinism It may also occur with large nonpancreatic tumors, heart failure, Simmond s disease, and factitious hyperinsulinism (T–48, 49 52, 56–61) Spontaneous hypoglycemia may be an early manifestation of diabetes mellitus (T–59)

Levels greater than 180 mg per cent after eating strongly suggest diabetes mellitus It is particularly important to check the blood level in diabetics if serious renal disease is present since the urine reductions can be very misleading

Glucose Tolerance Test—Oral (137)

NORMAL RANGE The maximum rise (in 90 to 120 minutes) should be less than 180 mg per cent and usually returns to or below the fasting level in 180 minutes

The upper limits of normal in the oral glucose tolerance test by the ' true glucose methods of blood sugar analysis are 150 mg per cent at 1 hour and 100 mg per cent at 2 hours (corresponding to 170 mg per cent and 120 mg per cent by the Folin Wu method respectively) (Also see Section II, p 687)

TECHNICAL NOTES 100 gm glucose is ingested by mouth Follow up for 6 hours with blood sugar determinations if hypoglycemia is anticipated This method is preferred to the Exton Rose (one hour, two-dose) method The patient should have consumed at least 200 gm carbohydrate on the previous two days A useful modification of the glucose tolerance test consists in the ingestion of the glucose meal at 8 a m , followed by blood sugars and urine tests at 9 a m and 10 30 a m

There are a number of gastrointestinal factors which may influence the validity of the 2-hour oral glucose tolerance test These consist chiefly of variations in the emptying time (particularly if the patient is made nauseated by the glucose) and variations in the time of intestinal absorption Since duplicate oral glucose tolerance tests can be obtained in only 75 per cent of normal subjects on whom two or more such tests are performed, and since modest elevations of the 2 hour specimen in individuals with normal fasting blood sugars on one test cannot be regarded as specific for diabetes, the clinician should not stigmatize a normal individual with this diagnosis unless the classic glucose tolerance test is confirmatory at another time (T–255b)

CLINICAL CLUES *A hyperglycemic response* occurs in diabetes mellitus hyperthyroidism, hyperpituitarism, the Cushing syndrome, and starvation *A hypoglycemic response* occurs in adrenocortical insufficiency steatorrhea, and functional hyperinsulinism

Since a number of normal individuals tend to exhibit flat curves it may be

unreliable as a test of intestinal absorption When the possibility of an inadvertent gastroileostomy is raised following a subtotal gastric resection, a flat curve may aid in establishing this diagnosis (T-133b)

Glucose Tolerance Test—Intravenous (Concomitant Serum Inorganic Phosphorus and Potassium Are Optional) (120, 129)

NORMAL RANGE *The blood sugar rises normally as with the oral test* The serum phosphorus drops 20 to 25 per cent The serum potassium decreases on an average of 0 33 mEq per liter

TECHNICAL NOTES Blood is drawn every 30 minutes for 2 hours and again at 3 hours

CLINICAL CLUES This technique is occasionally helpful where abnormal results in the oral tests are suspected to be due to impaired intestinal or pancreatic function and to thyrotoxicosis A flat curve occurs only in malnutrition (due to the avid absorption of glucose by the muscles)

The serum phosphorus and serum potassium are *not* reliable tests in distinguishing hepatic diabetes from true diabetes Diabetics as a group have less of a drop in the serum phosphorus but marked individual variations occur (129) When in doubt patients with hyperglycemia and glucosuria should always be treated as diabetics

ADRENAL MEDULLA

(pp 21 to 23)

Histamine Test See "Provocative Tests" (p 828)

Methacholine (Mecholyl) Test See "Provocative Tests" (p 828)

Tetraethylammonium Test See "Provocative Tests" (p 829)

Regitine Test See "Therapeutic Diagnostic Tests" (p 811)

Retroperitoneal Pneumography See "X Ray Approaches" (p 803)

Plasma Pressor Amines (T-68c)

NORMAL RANGE Less than 3 5 microgm per liter of plasma of epinephrine-*like substance*

TECHNICAL NOTES A modification of the method of Weil Malherbe and Bone is currently used Elevated concentrations of the pressor amines might be caused by hemolysis hyperbilirubinemia, and the use of epinephrine-like substances in the treatment of either asthma or nasal congestion It is recommended that the blood catecholamine levels be determined in samples taken at two minute intervals after either the onset of the clinical paroxysm in a suspected case of pheochromocytoma or following the injection of histamine (T-68d)

CLINICAL CLUES The concentration of epinephrine-like substance is almost always less than 3 5 microgm per liter of plasma in essential hypertension even after the injection of histamine Increases in the blood pressor amines are encountered not only in pheochromocytoma but occasionally in renal insufficiency jaundice increased intracranial pressure and lymphoma If the blood level of pressor amines is not significantly elevated in a patient suspected of having a pheochromocytoma (i e more than 3 5 microgm of epinephrine like substance per liter of plasma) a diagnostic rise might be induced by the injection of histamine

Urinary Catechols (T-64)

NORMAL RANGE 20 to 40 gamma normal output per diem (⅘ is norepinephrine), or 2 to 14 gamma per 100 ml of urine (There is no significant difference between the sexes)

TECHNICAL NOTES *Chromatographic, biologic and fluorometric techniques* are employed Elevated levels of epinephrine and norepinephrine may not be manifest in the urine When blood assays of these substances become generally available, more accurate information can be obtained by following the blood titers

There are several manners in which the chemical determination of the urinary catecholamines can be improved These consist of the following (1) determination of the sum rather than the individual quantities of the epinephrine and norepinephrine that are present, (2) the running of an internal standard with each specimen *(3) the avoidance of vigorous exercise prior to the collection of the urine* specimen (which might increase the output of the catecholamines as much as sevenfold) and (4) the use of a preservative to prevent the destruction of the unstable catecholamines (117)

CLINICAL CLUES An excess of 60 gamma epinephrine per day is suggestive of a pheochromocytoma In some patients with primary anxiety states, however, the urinary catechols have been elevated (T-62b) Most investigators have not found higher levels of these substances in the urine in patients with essential hypertension *although an apparent false positive reaction has been encountered in* malignant hypertension

Urinary Response to Piperoxan (132)

NORMAL RANGE Patients with *essential hypertension including those in* whom false positive drops in the blood pressure are induced will demonstrate a diuretic effect (i e , the volume of the third urine collection exceeds that of the second)

TECHNICAL NOTES The fasting and recumbent patient is given 1 liter of 0 25 per cent solution of sodium chloride orally The urine is collected for three or four successive 30 minute intervals The usual dose of piperoxan (Benodiane) is given intravenously after the second collection of urine The blood pressure response *is concomitantly observed*

CLINICAL CLUES In patients with functioning pheochromocytomas the volume of the third specimen is usually substantially less than that of the second This test has the unique advantage of inducing normal diuretic responses in patients who show nonspecific depressor responses to piperoxan

ADRENAL CORTEX (130) (T-87 89)

(pp 12 to 16 and 28 to 30)

17-Ketosteroids (130)

NORMAL RANGE

AGE	MALES	FEMALES
10	1– 4 mg	1– 4 mg
20	6–21 mg	4–16 mg
30	8–26 mg	4–14 mg
50	5–18 mg	3– 9 mg
70	2–10 mg	1– 7 mg

TECHNICAL NOTES Two successive overnight 12 hour specimens should be obtained

CLINICAL CLUES These hormones represent the steroids that are predominantly elevated in the adrenogenital syndrome due to adrenocortical carcinoma or hyperplasia testicular interstitial cell tumor and ovarian tumors More than 30 mg daily suggests a carcinoma A marked reduction after cortisone suggests adrenal hyperplasia

Normal levels of these steroids and of the FSH in patients with hirsutism suggest the Stein Leventhal syndrome and ovarian hyperthecosis The 17 ketosteroids are decreased in hypothyroidism hypopituitarism and adrenocortical insufficiency

Comparative Blood Eosinophil Counts Before and After Corticotropin (107, 108, 114)

NORMAL RANGE The normal basal level is from 70 to 450 cells per cu mm Physiologic short-term and diurnal variations in the level may be related to pulmonic, splenic adrenocortical or adrenomedullary activity There is a tendency to a progressive eosinopenia during the intermenstrual period although the ovarian hormones in themselves are not eosinopenic The differential white cell count is apt to be an inaccurate indicator of the total number of eosinophils The eosinophil drop should exceed 50 per cent following corticotropin (25 units intramuscularly or following an intravenous infusion)

TECHNICAL NOTES The various modifications of the Randolph staining technique are satisfactory and less demanding than the older methods (123) The average from four chambers or after counting 800 cells in the smear is taken The results from freely flowing finger blood or from oxalated venous blood do not differ significantly In contrast to the results with corticotropin the use of epinephrine or ephedrine is of little value in the diagnosis of adrenal hypothalamic or pituitary disease

CLINICAL CLUES Little or no drop occurs in primary adrenal insufficiency A gradual response over several days may be noted in pituitary failure The daily curves of patients with Addison s disease resemble those obtained in groups without adrenal disease The finding of a normal or high eosinophil level during the first 24 to 48 hours after an operation suggests adrenocortical insufficiency (139)

Comparative Urinary Steroid Outputs After Corticotropin (114)

NORMAL RANGE The urinary 17 ketosteroids should increase 50 to 100 per cent The 17 hydroxycorticoids should increase 200 to 300 per cent

TECHNICAL NOTES When less refined preparations were available intravenous ACTH (25 units) over an 8-hour period was more reliable than the intramuscular route and was repeated over a 3 day period if pituitary failure was suspected In current practice however repository corticotropin can be administered intramuscularly (40 units twice daily) over a 3-day period The effects produced by this preparation on the urinary 17 ketosteroids and corticosteroids have proved even more conclusive than the use of intravenous corticotropin over a single 8-hour period (114)

CLINICAL CLUES Few or no changes ensue in primary adrenal insufficiency On the other hand a gradual response over 3 days may occur in pituitary insufficiency A hyperactive steroid response suggests hyperplasia The absence of a *significant* response suggests carcinoma

Cortisone Suppression Test (see Section XIV, p 812)

17-Hydroxycorticoids (135)

NORMAL RANGE Fasting plasma levels of 10 to 15 gamma per 100 ml are normal The 24 hour urinary output ranges from 1 to 10 mg (5 3 mg average)

TECHNICAL NOTES The urinary titers are measured after ACTH gel (see above), and after 100 mg of cortisone are given in four divided doses

The interpretation of the concentrations of the various adrenal steroids in the plasma must be considered in light of the fact that they represent the difference between the rate of secretion and the rate of either excretion or destruction of that compound Accordingly they may not be directly correlated with the function of the adrenal cortex The additional knowledge that there is normally a diurnal variation in the excretion of the corticosteroids, the 17 ketosteroids and aldosterone highlights the necessity for several determinations if misleading interpretations are to be minimized

CLINICAL CLUES These hormones represent the predominant steroids that are elevated in the Cushing syndrome A rise after both ACTH and cortisone suggests an adenoma A rise only after ACTH suggests hyperplasia (T-91) *Autonomous inflexible elevations occur in carcinoma*

Robinson Kepler-Power Water Test (133)

NORMAL RANGE The volume of one of the hourly specimens should exceed the night volume

TECHNICAL NOTES The volume of the night urine is measured The hourly urine output is then measured after the patient has been given 20 ml water per kg of body weight (9 ml per pound)

CLINICAL CLUES An impaired output occurs in adrenal insufficiency It may also be due to kidney, liver and intestinal disorders

Abstinence from Sodium Test (see Section XV, p 819)

X Ray Studies of the Adrenals

TECHNICAL NOTES Routine flat abdominal films and pyelograms are valuable for screening purposes *Tomograms and retroperitoneal pneumograms are* also occasionally helpful (p 803)

CLINICAL CLUES Calcification occurs in one fourth of the patients with *Addison s disease Of these only one half are due to tuberculosis, however (333)*

RIGHT ADRENAL

TECHNICAL NOTES Observe the descending duodenum as visualized in the right lateral recumbent position after the ingestion of barium (118)

CLINICAL CLUES This may be a valuable clue in determining enlargement of the right adrenal gland (which tends to displace the descending duodenum anteriorly)

LEFT ADRENAL

TECHNICAL NOTES Administer 6 to 10 oz of a carbonated beverage just before taking the late upright film during intravenous urography (122a)

CLINICAL CLUES This is a simple and valuable technique in evaluating a suspected enlarged left suprarenal shadow Since most such shadows are actually

due to an overlying empty stomach, this procedure may obviate the somewhat more hazardous retroperitoneal studies

Blood Sodium, Potassium, Chloride, and Carbon Dioxide (112)

NORMAL RANGE See Blood Chemistries ' (pp 685, 691 and 693)

CLINICAL CLUES Decreased sodium and elevated potassium levels occur in adrenocortical insufficiency An unexplained hypokalemia and alkalosis should suggest primary aldosteronism (T-94)

Urinary Aldosterone

NORMAL RANGE 4 to 8 microgm per 24 hours

TECHNICAL NOTES Considerable improvement over the present bioassay and chemical assay techniques will undoubtedly be forthcoming

The diurnal variations in the excretion of aldosterone in patients with true hyperaldosteronism may be sufficiently great so that the urine levels are occasionally normal Accordingly several determinations should be obtained if the results are equivocal

CLINICAL CLUES With salt restriction in various edematous states, the urinary titers may range from 4 to 50 microgm because of the secondary hyperaldosteronism effect Levels up to 200 microgm have been found in the presence of a primary aldosteroma Normal titers in this disease have been encountered however and do not exclude its presence

SECTION VI

Bacteriologic and Immunologic Studies

TEMPERATURE DETERMINATIONS

Temperature Recordings

TECHNICAL NOTES Oral temperatures of 100 are occasionally normal en in doubt or if the patient is unable to cooperate, rectal temperatures are re accurate The attendant should be present during the recording if malingering uspected or the temperature of a freshly voided urine specimen should be orded (T-369) One should avoid taking the temperature after a recent meal oking or exercise

CLINICAL CLUES See Part I for discussions of the various causes of obscure er (the infections the granulomata, the collagen diseases neoplasms, periodic ase impaired heat dissipation etc) (pp 104 to 109 322 and 412)

CULTURES AND BACTERIOLOGY

od (163)

TECHNICAL NOTES Aerobic and anaerobic cultures may be necessary cimens are best drawn just prior to or after a chill

arious media are utilized as indicated by the bacteriologist and the clinical ure A thioglycollate medium is preferred for anaerobic cultures Incubation n atmosphere of 10 per cent carbon dioxide may be necessary to isolate *Brucella tus*, *Neisseria gonorrhoea* and *N meningitidis* *Bacteroides* infection may be looked if associated with microaerophilic streptococci, or if not subcultured in ser s medium to which serum has been added (T-601) Culture of the blood (following lysis with streptokinase) has proved to be superior to the culture hole blood in the isolation of the typhoid and *Brucella* organisms (172)

lthough there is no advantage to arterial cultures, more positive results may btained from the vein directly draining a focus of infection This is particularly iane when a bacterial endarteritis complicating an acquired arteriovenous la is suspected (T-421) Cultures should never be discarded as 'negative re three weeks

linicians should realize that many laboratory technicians may mislabel *Staphy cus aureus* cultures as *S albus* because the cultures are not observed long igh Furthermore some coagulase-positive staphylococci do not produce nent

ained and unstained smears for the malarial parasites should be examined n the possibility of malaria as a cause of undetermined fever exists

The serum which is being stored for subsequent viral immunologic studies should be kept at 40 C until it is used

All specimens for virus isolation must be frozen immediately upon collection (preferably by immersion in a mixture of dry ice and alcohol or by placing them in a quick freeze box) and kept so during shipment to the laboratory If freezing is impossible tissue specimens may be placed in buffered glycerine-saline solution

The following animals are used for isolating viruses suckling mice—Coxsackie herpes simplex and dengue adult mice—the arthropod borne encephalitides lymphocytic choriomeningitis rabies yellow fever, and the psittacosis-lymphogranuloma venereum group guinea pigs—lymphocytic choriomeningitis embryonated hen s eggs—herpes simplex variola vaccinia mumps and influenza

The highest yield of virus isolation from the various tissues in tissue cultures is obtained when the material used for the inoculation is taken either during the prodromal phases of the infection or in the early phases of the disease Certain viruses (as those of herpes simplex, poliomyelitis and the Coxsackie viruses) may be recovered weeks or months after the patient s recovery (150b)

Clinical Clues In endocarditis most of the positive cultures can be obtained within 48 hours and from the first 4 or 5 specimens (T–410-412) See Group IV of Part I for the significance of positive and negative cultures in cases of prolonged sepsis (p 116) In patients with active brucellosis, an average of 7 blood cultures may be needed to ensure at least 1 positive culture in the pretreatment observation period (T–560c)

Urine

Technical Notes A catheterized specimen is usually needed in females The pour plate technique and quantitative counts may be of equal importance (T–398) (See Section III p 111) Urinary antiseptics should be omitted for 24 to 48 hours whenever possible

Great care should be exerted in collecting specimens from male patients since a significant number of organisms are normally found within the first 4 cm of the urethra (156)(T–397) Urethral contamination in the male is best avoided by use of the two-glass technique In collecting specimens it is important that the urine be left in the bladder sufficiently long for the infecting organisms to be drained and multiplied

Clinical Clues Bacteriuria may be more significant than pyuria Tuberculosis should be suspected if pyuria is constant and if the cultures repeatedly show no growth For practical clinical purposes the gram stain of the freshly collected and unsedimented urine will differentiate contamination from infection (162)

Stools

Technical Notes Specimens may be collected directly from the stool by rectal swab (of great value in the rapid screening of large groups) and through a proctoscope or sigmoidoscope Portions of blood pus or mucus must be included if these are present Careful study for *Entamoeba histolytica* and differentiation from *Entamoeba coli* in fresh warm stools is essential The use of soapsuds enemas is specifically contradicted prior to the obtaining of specimens to be examined for *E histolytica* No preparation is required if diarrhea is present There have been many occasions on which a trained parasitologist was fooled by macrophages simulating trophozoites and yeasts simulating the cysts of *E histolytica* One should smear and culture for staphylococci enteric bacilli and other organisms employing the media as indicated Authentic stools are checked by giving the patient lycopodium spores to ingest and searching for their presence It must be borne

in mind that the culture media employed for the pathogenic enteric bacilli will destroy or obscure the growth of the gram positive cocci

CLINICAL CLUES Antibiotic resistant staphylococci may cause pseudomembranous enterocolitis Typhoid carriers among relatives and food handlers should be sought out in an endemic Roundworm infestation should be looked for in obscure anemias affecting patients in the warmer climes One should bear in mind that several types of *Salmonella* organisms are present in a significant per centage of patients who have salmonellosis (T–592c)

Sputum

TECHNICAL NOTES Deep secretions must be obtained No preservative should be used Concentrated 24-hour specimens are more rewarding if tuber culosis is suspected It is wise to culture sputum or gastric specimens on two dif ferent media, such as Lowenstein s and Petragagni s media, particularly when dealing with outpatient cultures (173a)

There are many factors which interfere with the recovery of tubercle bacilli, including small numbers of organisms in the specimen, the digestant material (which may destroy 80 per cent of the viable organisms) variations in either tem perature (above or below 30° C) or pH (above or below 7) bactericidal by products of vitamin C in the urine, and the presence of antibiotics The value of three daily, properly cultured gastric specimens in the diagnosis of tuberculosis remains time proven

Fungal studies are frequently very helpful especially the periodic acid stain, Sabouraud s medium, and India ink (to demonstrate the capsules) (151, 164) A good smear may be more revealing than cultures Great care should be taken to prevent a laboratory acquired infection

CLINICAL CLUES It is a wise habit for the physician always to examine *personally* the sputum of a patient who is seriously ill with pneumonia, particularly when the cause is obscure Fungal infections can often be first diagno ed in the sputum, especially blastomycosis Monilia is usually only an incidental saprophyte The overgrowth of the red pigmented *Serratia marcescens* (*Bacillus prodigiosus*) in the respiratory tract of patients with chronic lung disease may simulate hemop tysis (T–487c) It is not generally appreciated that the presence of large numbers of eosinophils in the sputum can macroscopically simulate the appearance of pus

Skin

TECHNICAL NOTES One should culture for the Klebs-Loeffler bacillus the tubercle bacillus other bacteria and fungi in chronic cutaneous lesions Freshly exuding pus is best examined after withholding local treatment The smear should be dried rapidly to prevent shrinkage of cells

Fungal studies may be facilitated by using a modified Sabouraud s medium an ink potassium hydroxide stain (made by mixing equal parts of 20 per cent potas sium hydroxide solution and Parker Super Chrome blue-black ink) or the periodic acid-Schiff stain (preferred for moniliasis and nonfluore cent ringworm) (151, 168) When prompt delivery of specimens for mycotic studies is not possible, one should employ Sabouraud s dextrose agar slants in screw capped tubes containing the inoculated material, rather than using Petri dish cultures or cotton tipped swabs

CLINICAL CLUES Lupus vulgaris leprosy syphilis, fungal infections and cutaneous diphtheria are very important causes of infectious dermatitis in the warmer climes (p 160) *Pseudomonas* bacteremia frequently results in metastatic skin lesions from which the organism may be cultured (T–481)

Gastric Secretions

TECHNICAL NOTES Direct smears are subject to much diagnostic error Special media is used for tubercle bacillus employing a processed concentrate of stomach washings

CLINICAL CLUES This time-tested technique is often helpful in the diagnosis of tuberculosis even when the chest films are negative and hematogenous spread is occurring

Bone Marrow

TECHNICAL NOTES Special culture media should be employed for brucellosis tuberculosis and the fungus infections as indicated The stained smear should be examined carefully

CLINICAL CLUES Very helpful in positively identifying the organisms causing typhoid fever hematogenous tuberculosis histoplasmosis, brucellosis, and other systemic infections (29)(T-533 560, 605) This is attributed to the greater concentration in the marrow of macrophages containing these visible organisms

Tonsils-Pharynx

TECHNICAL NOTES One should attempt to collect secretions from the underlying tissue surface of the affected area An attempt to culture *Corynebacterium diphtheriae* must always be made if in doubt about the nature of an acute membranous pharyngitis One should also stain for the Vincent organisms with 2 per cent crystal violet in methyl alcohol

Nutrient broth or buffered isotonic saline solution to which 10 per cent rabbit serum has been added are the best media for throat and nasopharyngeal washings prior to their inoculation onto tissue cultures When nasopharyngeal washings serum cerebrospinal fluid or other body tissues and excretions are to be inoculated into tissue cultures or animals they should be placed in an insulated cabinet containing carbon dioxide ice while being shipped

CLINICAL CLUES Diphtheria is *not* a rare disease particularly in the aged (T-581 582) Infectious mononucleosis should be considered when a membrane is present in the face of negative cultures (T-725) The Vincent organisms are of significance *only* in the presence of pathologic lesions

It may be possible to differentiate the pharyngitis caused by hemolytic streptococci and that due to viruses short of bacteriologic analysis by an examination of the pharyngeal exudate (174) The predominance of neutrophils in the former contrasts with the mononuclear-cell exudate of viral infections

Liver

TECHNICAL NOTES When indicated cultures are carried out simultaneously with histologic studies (See p 716 for technique)

CLINICAL CLUES Very helpful in the early diagnosis of hematogenous tuberculosis histoplasmosis brucellosis and schistosomiasis (T-534 563 605 629 631)

Transfusion Blood

TECHNICAL NOTES Direct smears and cultures should be taken from the unit of the suspected whole blood when a transfusion reaction with fever has

occurred See page 462 for a safe technique of detecting bacterial contamination using plastic equipment (T-1288b)

CLINICAL CLUES Fatal transfusion reactions may be due to contamination of stored blood with gram negative organisms that grow in the cold (T-1285-1288)

Cerebrospinal Fluid

TECHNICAL NOTES One should look for the torula organisms in a chronic nontuberculous lymphocytic meningitis (T-608) *Cryptococcus neoformans* should not be confused with red cells Chocolate agar cultures (particularly for *Hemophilus influenzae*) and other media are used as indicated Except in the case of suspected mumps cerebrospinal fluid need not be submitted for virus isolation studies (T-566b)

CLINICAL CLUES An associated lymphoma should be sought when torulosis is present (T-609) Tuberculosis must be considered if the smears are negative in the presence of a meningitis

"Sulfur Granule"

TECHNICAL NOTES These bodies may be produced by infections other than actinomycosis Look for the typical filaments on Gram's stain

CLINICAL CLUES Differential cultures are necessary since the aerobic and anaerobic actinomycetes are not susceptible to the same antibiotics or sulfonamides (p 168) (T-614 615)

Differentiation of Acid Fast Bacilli (T-547, 548)

TECHNICAL NOTES Observations are made relating to growth in egg or potato media growth in fresh meat extract blood agar at various temperatures and at various carbon dioxide concentrations color production of the colonies resistance or sensitivity to PAS, INH, and streptomycin emulsification in broth or saline virulence in guinea pigs and sensitization of these animals to tuberculin

CLINICAL CLUES This differentiation may be very important in arriving at a diagnosis of a nontuberculous infection The tubercle bacillus is characterized by slow growth in the conventional egg or potato media before well developed colonies are formed dry dull and crumbly colonies poor emulsification in broth or saline solution little or no yellow pigment sensitivity to PAS INH, and streptomycin in patients not receiving chemotherapy and virulence in guinea pigs This is in striking contrast to the so called saprophytic acid fast bacilli (p 153)

SERUM IMMUNOLOGIC TESTS (149, 150, 151c 155)

General Comments

TESTS AND TECHNICAL NOTES In obscure acute infections serum should be drawn during *both* the acute and convalescent phases in order to detect significant changes in titers For serologic studies blood serum (not plasma) should be separated from the clot before shipment in order to prevent gross hemolysis

SIGNIFICANT TITERS AND CLINICAL CLUES A significant titer is usually indicated by at least a fourfold increase over that of the earlier specimen A rising titer may be of greater value than one single high titer The anticomplementary activity of serum (due to either syphilis other causes for biologic false-positive reactions or to bacterial contamination) may render accurate complement fixation determinations difficult (150b)

Adenovirus (Adenoidal Pharyngeal Conjunctival Disease)

TESTS AND TECHNICAL NOTES Complement fixation (group-specific) Neutralization (type-specific)

SIGNIFICANT TITERS AND CLINICAL CLUES Diagnostic rises can be detected in 2 to 3 weeks The virus has been isolated from the pharynx, the sputum the conjunctival sac, or the saliva by tissue culture in HeLa cells

Amebiasis

TESTS AND TECHNICAL NOTES Complement fixation test Immobilization of *Entamoeba histolytica* by a rabbit antiserum (experimental at present, but holds clinical promise) (T–618b)

SIGNIFICANT TITERS AND CLINICAL CLUES Differences of opinion exist concerning the value and reliability of the complement fixation test In one review of 1370 patients on whom the complement fixation test had been performed, the test was positive in 17 5 per cent of the patients with intestinal amebiasis (T–618a) The immobilization technique may prove useful in detecting carriers and in differentiating the various amebas in the human intestine (T–618b) False-positives have been noted in cat-scratch disease

Brucellosis

TESTS AND TECHNICAL NOTES Agglutination test (There may be cross agglutination with *Pasturella tularensis* and *Vibrio cholerae*) The opsonocytophagic test is a complicated impractical and usually unrewarding procedure (171) When 'blocking antibodies are suspected in a probable case of chronic brucellosis in which only very low titers of agglutinins can be demonstrated a significant titer might be obtained by simply centrifuging the tubes (15 minutes at 3000 r p m) at the end of the routine agglutination test (T–560e)

SIGNIFICANT TITERS AND CLINICAL CLUES A titer of at least 1 80 to 1 320 is usually necessary The procedure is unreliable if a recent skin test with brucellergen has been performed It may be negative in the presence of an active infection due to the prozone phenomenon or to blocking antibodies (T-560)

Coccidioidomycosis (pp 166 and 552)

TESTS AND TECHNICAL NOTES Complement fixation test Precipitin test (more transient)

SIGNIFICANT TITERS AND CLINICAL CLUES This study should be performed in the presence of pulmonary lesions with thin walled cavities, few symptoms and a negative tuberculin test A rise in titer above 1 16 to 1 32 may indicate spread and a poor prognosis The complement fixation test becomes positive in the non disseminating cases after the skin and precipitin tests (T-604) It appears in the spinal fluid only if meningitis develops

Coxsackie Virus Infection (p 136) (Type A—19 Subtypes, Type B—5 subtypes)

TESTS AND TECHNICAL NOTES Neutralization tests (in suckling mice) Complement fixation tests (not recommended due to the development of heterotypic antibody elevations)

SIGNIFICANT TITERS AND CLINICAL CLUES A significant rise in the titers of acute to convalescent sera is considered diagnostic Infections caused by strains

of Type A are mainly associated with herpangina Strains of Type B are usually responsible for epidemic pleurodynia and for some cases of aseptic meningitis (157)

Cysticercosis (pp 175 and 368)

TESTS AND TECHNICAL NOTES Complement fixation test (An alcoholic extract of *Taenia solium* is used)

SIGNIFICANT TITERS AND CLINICAL CLUES The specificity of this antigen is not absolute Accordingly, positive reactions may not be conclusive, while a negative test does not exclude the diagnosis It may be of great value, however in the patient with *evidence of an expanding intracranial mass and an associated* eosinophilia in the blood and spinal fluid (T–633)

Dengue

TESTS AND TECHNICAL NOTES Complement fixation test Neutralization test

SIGNIFICANT TITERS AND CLINICAL CLUES *The complement fixation test* becomes positive in 2 to 3 weeks The neutralization test becomes positive in 7 days and may persist so for several years The virus can be isolated from the blood by intracerebral inoculation into 1- to 3-day old mice

Enteric Cytopathogenic Human Orphan (ECHO) Viruses (p 136)

TESTS AND TECHNICAL NOTES Neutralization in tissue culture

SIGNIFICANT TITERS AND CLINICAL CLUES This test becomes positive in 5 to 7 days The viruses may be isolated from the pharynx, the stool or even the spinal fluid by culture in HeLa or monkey kidney cells They are known to be a cause of lymphocytic or aseptic meningitis (T–473) There have already been 14 antigenic types of ECHO viruses identified *Unlike that of the Coxsackie family*, the pathogenicity of these viruses in suckling mice or other animal species has not as yet been demonstrated

Gonorrhea

TESTS AND TECHNICAL NOTES Complement fixation test

SIGNIFICANT TITERS AND CLINICAL CLUES This test is not generally reliable in polyarthritis, pelvic inflammatory disease, chronic prostatitis and gonococcemia because of the many false-positive and false negative results (T–557, 578)

Herpes Simplex (pp 160 and 522)

TESTS AND TECHNICAL NOTES Complement fixation test Neutralization *in mice or chick embryos*

SIGNIFICANT TITERS AND CLINICAL CLUES The serologic tests become positive within 5 days of the clinical infection They may persist so for many years or even for life The presence of multinucleated giant cells in *the skin lesions can* also aid in the diagnosis if further confirmation is needed (282 299)

Histoplasmosis (pp 124 and 167)

TESTS AND TECHNICAL NOTES Complement fixation test

SIGNIFICANT TITERS AND CLINICAL CLUES A high antibody response gen

erally indicates a good prognosis while a low antibody titer signifies a poor prognosis Serial skin testing of a positive reactor will increase the titer (T-605 606)

Infectious Mononucleosis (p 198)

TESTS AND TECHNICAL NOTES Heterophile-antibody agglutination, with differential absorption by guinea pig kidney and beef red blood cells

The ox erythrocyte hemolysin technique is perhaps more sensitive than the agglutination of sheep erythrocytes High titers of a hemolysin to ox erythrocytes can usually be demonstrated within the first week in patients with infectious mononucleosis They often persist until the sixth week The red cell and guinea pig kidney absorption characteristics of this hemolysin to ox erythrocytes resemble those of the heterophile antibody of Bunnell (T-732b)

SIGNIFICANT TITERS AND CLINICAL CLUES The rise in titer may be delayed as long as 2 months A titer of at least 1 32 occurs in 50 to 80 per cent of cases with the antigen being absorbed only by beef red blood cells This test should be performed in atypical cases of sore throat fever neurologic complications and hepatitis (T-725)

Occasional false-positive reactions occur in lupus erythematosus thrombohemolytic thrombocytopenic purpura, after horse serum injections and even in normal individuals These can be separated by the absorption studies False positive reactions may also be produced by cold agglutinins but these can be dispelled at 37 C On rare occasions positive tests cannot be found in cases of probable infectious mononucleosis (T-732)

Influenza (p 125)

TESTS AND TECHNICAL NOTES Hemagglutination inhibition test Complement fixation test Neutralization test

SIGNIFICANT TITERS AND CLINICAL CLUES At least a fourfold rise in either test is necessary (Failure to demonstrate the rise in titer may be due to the late collection of the convalescent specimen)

Leptospirosis (p 157)

TESTS AND TECHNICAL NOTES Agglutination test The presently available tests of agglutination agglutination lysis and complement fixation are type specific, and consequently laborious for routine screening purposes Recently there have been developed stable antigens of sufficiently broad sensitivity to detect antibodies produced against all serotypes of *Leptospira* (152)

SIGNIFICANT TITERS AND CLINICAL CLUES This study may elucidate the cause of certain obscure cases of benign aseptic meningitis (T-473) A titer of at least 1 1000 is diagnostically conclusive The agglutinins may persist for years

Lymphocytic Choriomeningitis (p 135)

TESTS AND TECHNICAL NOTES Neutralization test Complement fixation test

SIGNIFICANT TITERS AND CLINICAL CLUES A neutralization index of 50 and a complement fixation titer of 1 8 to 1 64 are considered diagnostic The finding of more than 600 lymphocytes per ml in the cerebrospinal fluid is suggestive of this disease in the presence of an aseptic meningitis (T-473) The neutralization test in lymphocytic choriomeningitis may persist positive for many years

Lymphogranuloma Venereum (p 155)

TESTS AND TECHNICAL NOTES Complement fixation test (Cross complement fixation occurs in psittacosis)

SIGNIFICANT TITERS AND CLINICAL CLUES A titer of only 1 4 may be significant The test remains positive as long as the virus is in the host The titer is not influenced by prolonged sulfonamide therapy (T-556 558) Many patients with cat-scratch disease develop a positive complement fixation reaction to the lymphogranuloma antigen (T-643b) The lymphogranuloma venereum virus can be isolated from bubos lymph nodes or anorectal tissue by growth in the yolk sac of the embryonated chick or by the intracerebral inoculation of mice

Mumps (p 158)

TESTS AND TECHNICAL NOTES Complement fixation test Hemagglutination inhibition test (Normal sera frequently exhibit considerable hemagglutination inhibition)

SIGNIFICANT TITERS AND CLINICAL CLUES A titer of 1 64 or a fourfold increase, respectively are considered diagnostic This is an important test in cases of unexplained aseptic meningitis labyrinthitis, Bell s palsy, and orchitis in adults (T-473 566) The antigen used in skin testing stimulates antibody production The serologic tests may remain positive for several months following clinical mumps

The virus can be isolated from the saliva by injection into monkeys or by culture in the amniotic sac of embryonated hen s eggs early in the course of the disease

North American Blastomycosis (p 167)

TESTS AND TECHNICAL NOTES Complement fixation test

SIGNIFICANT TITERS AND CLINICAL CLUES The presence of a high titer and a negative skin test denotes a poor prognosis A low or absent titer and a positive skin test usually indicate a good prognosis (T-612 613)

Poliomyelitis (p 134)

TESTS AND TECHNICAL NOTES Neutralization test Complement fixation test (Antigens of the several strains are prepared from virus grown in tissue culture The neutralization test requires about one week Blood samples must be tested separately against all three major types of the virus)

SIGNIFICANT TITERS AND CLINICAL CLUES These are primarily epidemiologic research tools at present Although less expensive and less time-consuming the reliability of the complement fixation test has yet to be demonstrated (It is well to recall that more than 500 lymphocytes per ml in the spinal fluid are infrequently found in this disease)

Primary Atypical Pneumonia (p 125)

TESTS AND TECHNICAL NOTES Cold hemagglutinin test *Streptococcus MG* agglutination test

SIGNIFICANT TITERS AND CLINICAL CLUES Titers of at least 1 128 and 1 20, respectively, are considered diagnostic Cold hemagglutinins are also found in mumps, hemolytic anemias, various liver diseases certain peripheral vascular diseases and in the common respiratory diseases(154) but not in adenovirus infec

tion Their appearance may be delayed by antibiotic administration (T-440) *Streptococcus MG* agglutinins appear to be fairly specific for this disease, but are found in only half of the patients

Psittacosis-Ornithosis (p 161)

TESTS AND TECHNICAL NOTES Complement fixation test (Cross-complement fixation with lymphogranuloma venereum may occur)

SIGNIFICANT TITERS AND CLINICAL CLUES A titer of at least 1 16 with a fourfold rise is considered diagnostic This study may be a very important consideration in the presence of a severe protracted atypical pneumonia (T-587 589) (No cold agglutinins are produced by these viruses)

Q Fever (p 125)

TESTS AND TECHNICAL NOTES Agglutination test Complement fixation test

SIGNIFICANT TITERS AND CLINICAL CLUES Titers of at least 1 8 and 1 20 within 4 weeks respectively are highly specific No Weil Felix reaction occurs Sera with cold *agglutinins do not react with the Q fever antigen* (T-442)

Rickettsialpox (p 551)

TESTS AND TECHNICAL NOTES Complement fixation test (Cross-complement fixation with R M S F may be obviated by using washed rickettsiae as the homologous antigen)

SIGNIFICANT TITERS AND CLINICAL CLUES A titer of at least 1 10 is required for diagnosis No Weil Felix reaction occurs in this disease

Rocky Mountain Spotted Fever (p 162)

TESTS AND TECHNICAL NOTES Weil Felix agglutination test with Proteus OX 19 and OX 2 Agglutination test Complement fixation test (Cross-complement fixation may occur in rickettsialpox)

SIGNIFICANT TITERS AND CLINICAL CLUES Titers of at least 1 320 1 4 and 1 10 respectively are considered diagnostic They begin to become positive about the tenth day and may remain positive for years Antibiotics can interfere *with or prevent the formation of complement-fixing antibodies* but *without* affecting the Weil Felix response

Salmonellosis (p 163)

TESTS AND TECHNICAL NOTES Agglutination tests (Most commercial sera do not detect antibodies to the somatic antigens of Groups B C D and E)(T-593) (Refer to Part I)

SIGNIFICANT TITERS AND CLINICAL CLUES A bacteremia with embolic abscesses occurs very commonly in this group of diseases with or without an associated gastroenteritis (T-592-596)

Scrub Typhus

TESTS AND TECHNICAL NOTES Weil Felix agglutination test with Proteus OX K Complement fixation test

SIGNIFICANT TITERS AND CLINICAL CLUES Titers of at least 1 160 and 1 10, respectively, are considered diagnostic Leptospirosis may also give rise to OX K agglutinins

St Louis Encephalitis (Eastern or Western Equine Encephalitis) (p 137)

TESTS AND TECHNICAL NOTES Complement fixation test (using mouse brain as antigen) Neutralization test in mice

SIGNIFICANT TITERS AND CLINICAL CLUES The complement fixation test becomes positive in 4 days to 4 months The neutralization test becomes positive in 1 to 2 weeks and may remain so for up to 4 years The virus can be isolated from the brain by intracerebral inoculation into mice

Syphilis (I) (pp 136 and 154)

TESTS AND TECHNICAL NOTES Complement fixation test Precipitin tests

SIGNIFICANT TITERS AND CLINICAL CLUES A positive serology is occasionally the first clue to lupus erythematosus myeloma and infectious mononucleosis (T–554 555) It may be negative in 10 to 20 per cent of patients with tertiary syphilis (T–553) Other significant causes of false positive reactions include leprosy, spirochetal infections (leptospirosis rat-bite fever relapsing fever), infectious hepatitis, lymphogranuloma venereum vaccinia upper respiratory infections, acute malaria and typhus

Syphilis (II)

TESTS AND TECHNICAL NOTES *Treponema pallidum* immobilizing test and its simpler modifications (viz , T P complement fixation, T P agglutination, T P immune-adherence) The advantages of the T P immune-adherence test are as follows the specificity and sensitivity are at least equal to those of the T P I test considerable amounts of the antigen can be prepared and stored since heat-killed treponemes are employed the antigen remains stable for at least 6 months only 5 hours are required to complete the test (in contrast to 2 days for the T P I test) and anaerobic facilities are not necessary (166)(T–555)

SIGNIFICANT TITERS AND CLINICAL CLUES Very helpful in detecting the biologic false-positive reactors in neurosyphilis or cardiovascular syphilis when confronted with negative blood and spinal fluid serologies and in mothers with negative serologies whose children develop the stigmata of congenital syphilis (T–555) It may aid in the differential diagnosis of rheumatic or rheumatoid aortic valvulitis (T–976) This test cannot be u ed as a guide for treatment however After refrigeration and storage some initially positive specimens may become negative

Toxoplasmosis (p 172)

TESTS AND TECHNICAL NOTES Neutralization test Complement fixation test Cytoplasm modifying test with dyes (Sabin)

SIGNIFICANT TITERS AND CLINICAL CLUES May be diagnostic in an acute encephalitis or chorioretinitis of obscure origin (T–634) A toxoplasmin dye test titer of at least 1 64 is usually indicative of active ocular toxoplasmosis (T–635) In such cases, there is an 80 per cent correlation between the skin and dye tests The complement fixation reaction is of little value unless it develops during the course of an acute infection

Tularemia (p 122)

TESTS AND TECHNICAL NOTES Agglutination test (Cross agglutination with the brucella organisms may occur)

SIGNIFICANT TITERS AND CLINICAL CLUES A titer of at least 1 80 is required It may remain elevated up to 1 year after immunization

Typhoid Fever (p 163)

TESTS AND TECHNICAL NOTES Agglutination tests for the O ' H and Vi antigens

SIGNIFICANT TITERS AND CLINICAL CLUES Concomitant O and H titers of 1 80 or above might signify infection (unless the patient has been recently immunized) An elevated H titer alone is usually of no significance 'Vi agglu tinations occur in 80 per cent or more of typhoid carriers

Typhus (Epidemic and Murine) (p 162)

TESTS AND TECHNICAL NOTES Weil Felix agglutination test with Proteus OX 19 Agglutination test Complement fixation test

SIGNIFICANT TITERS AND CLINICAL CLUES Titers of at least 1 160, 1 40 and 1 10 respectively are considered diagnostic They are not increased by fevers of nontyphus origin These tests begin to become positive about the eighth day and may remain positive for years

SKIN TESTS

General Comments

TECHNICAL NOTES If great sensitivity to a substance is suspected smaller dilutions should be used Usually 0 1 ml is injected into the skin on the flexor surface of the forearm A control should be employed whenever possible

CLINICAL CLUES The diagnosis of active infection by skin tests is best made when a previously negative response becomes positive Negative tuberculin tests or positive Schick and Dick tests after known previous antigenic stimulation may occur in hypogammaglobulinemia (p 145)

Blastomycin (North American) (p 167)

TECHNICAL NOTES The 1 1000 dilution is preferred A histoplasmin skin test should also be performed if the test is positive A positive reaction should be confirmed by a smear and culture of the exudate

CLINICAL CLUES A positive reaction in 48 hours indicates previous infec tion It may be negative in advanced cases with a high complement-fixation titer Cross immunity with histoplasmosis may occur (T–612)

Brucellergen (p 156)

TECHNICAL NOTES The antigenic material may consist of either nonviable *Brucella* organisms or their nucleoprotein fraction The test should be read in 48 hours

CLINICAL CLUES A positive reaction indicates previous or present infec tion The test is negative however in from 5 up to 39 per cent of individuals with the chronic disease It may also be negative when high agglutinin titers and

even positive blood cultures are present. This test stimulates agglutinin and opsonin production and accordingly should be delayed until the agglutination titers have been checked (171)(T-560).

Cat Scratch Disease Antigen (p. 177)

TECHNICAL NOTES. Treated antigen from the pus of affected lymph nodes is employed. *The test should be read in 48 hours.*

CLINICAL CLUES. A papule exceeding 0.5 cm. will occur in most cases of this disease. Positive tests occur *in up to 10 per cent of the controls, possibly* due to previous mild infections (165).

Coccidioidin (p. 166)

TECHNICAL NOTES. An extract of the growth of *Coccidioides immitis* in broth is used. Dilutions of 1:1000 or 1:100 are employed. Inconstant cross reactions with the antigens of the histoplasmosis and blastomycosis organisms occur. This skin test is more important as a screening procedure than the serologic studies.

CLINICAL CLUES. A positive reaction indicates previous infection. It usually becomes positive one month after exposure (or a week after symptoms develop) and precedes the serologic tests in the nondisseminating cases (T-604). Only one out of four positive reactors gives a history suggestive of the acute disease.

Dick Test

TECHNICAL NOTES. Erythrogenic streptococcus toxin. The test should be *read in 24 hours.*

CLINICAL CLUES. A positive reaction usually indicates susceptibility to the erythrogenic toxin of the beta hemolytic streptococcus. One must evaluate pseudo reactions with reference to the control reaction.

Echinococcus Antigen (p. 174)

TECHNICAL NOTES. The Casoni *or substitute antigen (0.25 ml.) is used.* A saline control should also be employed.

CLINICAL CLUES. A positive reaction (immediate or delayed) indicates previous infection. False-positives may be due to a hypersensitivity to sheep serum, *or to infestation with other cestodes. The skin test is more reliable than the com*plement fixation test or the precipitin test (*vide supra*).

Enders Test for Mumps (p. 158)

TECHNICAL NOTES. *Inactivated mumps virus. The test should be read in* 24 and 48 hours.

CLINICAL CLUES. A positive reaction indicates immunity and often persists for life. It is particularly useful in evaluating parotitis and orchitis in adults since it does *not* become positive until several weeks have elapsed after the onset of the mumps infection (T-566).

Frei Test for Lymphogranuloma Venereum (p. 155)

TECHNICAL NOTES. Inactivated lymphogranuloma venereum virus (ly

granum antigen) The test should be read in 48 hours Induration may be more significant than the erythema particularly in colored patients

CLINICAL CLUES A positive reaction indicates previous infection and lasts for years A negative reaction does not exclude active infection (T–557)

Ito-Reenstierna Test for Chancroid

TECHNICAL NOTES Heat-killed chancroid bacilli The test should be read in 48 hours

CLINICAL CLUES A positive reaction indicates previous infection with chancroid and may last for many years Although the test is uniformly positive at the time the buboes appear a Frei test blood serology tests for syphilis dark field studies, and biopsies may still be necessary for accurate diagnosis

Histoplasmin (p 166)

TECHNICAL NOTES An extract of *Histoplasma capsulatum* growth in a synthetic broth is used The 1 1000 dilution is preferred

CLINICAL CLUES A positive reaction indicates previous infection The test becomes positive 1 month after exposure It is useful in epidemiologic studies and in evaluating pulmonary lesions in the presence of a negative tuberculin test It may become negative in a fulminating case of the disease (T–605 606) A cross reaction to blastomycin occurs in 50 per cent of these cases and to coccidioidin in a lesser degree

Lepromin (The Mitsuda Reaction) (p 176)

TECHNICAL NOTES The test material is prepared from lepromatous nodules (i e treated with phenol boiled and suspended in saline) A positive reaction takes the form of a small nodule that appears in two or three weeks

CLINICAL CLUES This test is primarily of prognostic value Patients with tuberculoid leprosy usually exhibit positive reactions while those with the lepromatous form of the disease demonstrate negative reactions The transformation of a negative reaction to a positive reaction in the latter type generally indicates a good therapeutic response (T–636 637)

It is important to be cognizant of the fact that positive reactions are noted in patients who neither have leprosy nor were ever exposed to it Much of this can probably be explained by a prior infection with one of the mycobacteria especially by *Mycobacterium tuberculosis* and as a result of BCG inoculation

Schick Test (p 160)

TECHNICAL NOTES Diphtheria toxin The test should be read in 48 and 96 hours

CLINICAL CLUES A positive reaction indicates susceptibility No critical level of antitoxin is measured by this test however and the immunity is only relative (T–581 582) Pseudoreactions also indicate probable immunity

Smallpox Vaccination

TECHNICAL NOTES The skin is pricked tangentially about 30 times One must be careful about both the technique itself and the use of a potent vaccine

CLINICAL CLUES A primary reaction (vaccinia) indicates lack of immunity An immediate reaction occurs if the individual is immune Complement fixation

and hemagglutinin inhibition studies for variola can also be performed, as well as study of the skin and mucous membranes for intracytoplasmic inclusions

Trichinella Antigen (p 173)

TECHNICAL NOTES The trichinella antigen is prepared from an extract of the larvae A 1 10,000 dilution produces fewer nonspecific reactions than the stronger concentrations

The hemagglutination test recently developed for the diagnosis of trichinosis is said to be 100 times as sensitive as the complement fixation test (T-621c)

CLINICAL CLUES Immediate and delayed reactions indicate previous infection The former becomes positive in the second or third week of the infection and usually remains positive for years The precipitin and complement fixation tests are also quite specific but may not become positive until the fifth week of the disease

Tuberculin (p 149)

TECHNICAL NOTES This test should be routine in *all* cases of prolonged fever particularly when Negroes and diabetics are affected Intracutaneous P P D or O T is employed The test should be read in 48 to 72 hours In infants, the patch method (Vollmer) is used the dose of the antigen corresponding to one midway between first and second strengths of O T (0 1 mg) Doses of 10 mg O T and double strength P P D #2 may be given if anergy is suspected

CLINICAL CLUES A positive reaction indicates previous infection Tuberculin sensitivity is usually maintained for long periods of time, having been encountered in many patients over 100 years of age (173b)

Hematogenous (miliary) tuberculosis only rarely produces anergy The limitations of the Mantoux test are pointed out by its negativity in up to 59 per cent of patients with suggestive roentgenographic changes of active or arrested pulmonary lesions Patients with chronic indolent pulmonary tuberculosis (from whose sputum the tubercle bacilli can be recovered) may manifest insensitivity to tuberculin (173c)

Other stated causes for the absence of such cutaneous reactivity are late pregnancy the puerperium and hypothyroidism Prolonged therapy of tuberculous children with INH has been associated with negative skin tests in some instances Cutaneous anergy may also occur in sarcoidosis, lymphoma (Hodgkin s disease) and hypogammaglobulinemia (T-652)

OTHER IMMUNOLOGIC STUDIES

Antistreptolysin O Titer

TECHNICAL NOTES The titer is expressed as the reciprocal of the highest serum dilution that completely neutralizes one combining unit of reduced streptolysin O

CLINICAL CLUES The presence of a high titer (400 units or more) is consistent with rheumatic fever—more so than with rheumatoid arthritis This is particularly true in children Titers less than 150 units are strong evidence against the diagnosis of active rheumatic fever (169) The height of the titer cannot be used to predict heart damage

C-Reactive Protein

TECHNICAL NOTES The patient s serum is added to a specific antiserum

incubated for 2 hours, and followed by overnight refrigeration The precipitation is graded from 0 to 6 +

Clinical Clues A precipitation is not produced by normal serum This test usually reflects a nonspecific response to inflammatory or infectious disease It is particularly useful as an index of rheumatic activity, especially since it is not depressed by heart failure It is negative in chorea minor, however (167) This test has also been demonstrated to be of value in the clinical management of acute myocardial infarction (158)

The Drop Latex Fixation Test

Technical Notes Latex particles in a stock suspension with a uniform mean diameter are mixed with borate buffer and gamma globulin Serum is then added to this mixture and the presence or absence of aggregation of the particles is noted A positive test is indicated by discernible aggregation

Clinical Clue This test has the obvious advantages of simplicity, inexpensiveness, and speed It is apparently as reliable as the currently used sheep cell agglutination tests for the detection of rheumatoid arthritis In one recent study, 84 2 per cent of 291 patients with rheumatoid arthritis showed positive latex fixation tests while 96 3 per cent of patients with rheumatic diseases other than rheumatoid arthritis gave negative reactions The infrequent false-positive tests occurred in patients with lupus erythematosus acute rheumatic fever, and in unclassified diffuse collagen disease

Gamma Globulin Test

Technical Notes A specific reaction normally occurs with antihuman gamma globulin serum The standard Coombs serum to which Coombs positive red blood cells are added can be used when an agammaglobulinemic state is suspected

Clinical Clues The reaction is absent in hypogammaglobulinemia (agammaglobulinemia) (T-525 530)

Pathogenicity Studies

Technical Notes Various techniques are employed including serologic staining, and animal injection methods in infection suspected to be caused by *Corynebacterium diphtheriae* *Mycobacterium tuberculosis* staphylococci and other organisms (bacterial viral rickettsial fungal)

Clinical Clues The alpha hemolysin titer is more discriminatory than the coagulase test in determining the pathogenicity of staphylococci (159)

Sensitized Sheep Cell Agglutination Reaction (160)

Technical Notes Agglutination is observed and titered after the addition of the patient s serum to sheep red cells which have been sensitized with a rabbit antisheep cell serum Various modifications can apparently enhance the specificity of this test, such as the elimination of the heterophile constituent of the test serum by absorption and the presence or absence of inhibition of this agglutination

Clinical Clues An agglutination titer 16 or more times greater than the titer for unsensitized cells is almost exclusively found in rheumatoid arthritis, particularly in the euglobulin fraction of the patient s serum Patients with this disease universally fail to show inhibition whereas over 96 per cent of the control subjects euglobulin fractions will cause this inhibition

Sensitivity Studies

TECHNICAL NOTES The ability of various antibiotics to inhibit the growth of cultured organisms is determined Although the "disc" method for antimicrobial sensitivity usually yields valuable results, the tube-dilution method gives more accurate information of a quantitative nature

Experience in Canada with the use of the antibiotic discs and tablets that are used so extensively in the determination of antibiotic sensitivity has pointed out the serious errors that might eventuate if they are not accurately labeled for potency in units or micrograms, or if they deteriorate as a result of careless handling and storage (153b)

CLINICAL CLUES These studies have become very important clinical considerations, particularly with reference to penicillin resistant staphylococci and the streptomycin resistant or INH resistant tubercle bacilli (153a)(T-486-491) Penicillinase production and clinical resistance of staphylococci to penicillin can be expected if the organisms are not affected by 0 15 units per ml

Clinical judgment in therapeutics, however may be more important inasmuch as the sensitivity studies might be misleading This is particularly so in bacteremias due to the *Proteus* organism and to *Aerobacter aerogenes* wherein streptomycin and a tetracycline antibiotic may be curative in spite of "streptomycin resistance" (T-597)

SECTION VII

Studies of Gastrointestinal Function

GASTRIC SECRETIONS AND FUNCTION

Volume

NORMAL RANGE The fasting volume should not exceed 50 ml

TECHNICAL NOTES The tube should be in the distal third of the stomach Continuous aspiration every 15 minutes for 1 hour is a simple and reliable measure of gastric secretion (200)

CLINICAL CLUES If more than a 300 ml residual is found 3 hours after the evening meal on two occasions or if clapotage (the gastric succussion splash) is demonstrated obstruction is present (T-1364) The gastric secretion in duodenal ulcer is usually high in gastric ulcer it is normal or even decreased Marked gastric hypersecretion should suggest the possibility of the Zollinger Ellison syndrome (p 20) (T-53)

pH

NORMAL RANGE A pH of less than 3 0 signifies the presence of free hydrochloric acid The lowest level obtainable is 0 9

TECHNICAL NOTES Indicator papers or the Beckman glass electrode may be used The pH meter is the most accurate method however

CLINICAL CLUES This is the only accurate way of detecting low levels of acidity A marginal ulcer can still occur if the pH is less than 5 The change in pH is a much more sensitive index of gastric secretion than is the measurement of free acid in units This stems from the fact that for every 1 unit change in pH there is a tenfold increase in the hydrogen ion concentration (211)

Free and Total Hydrochloric Acid

NORMAL RANGE The free acid should be greater than 30 to 50 degrees particularly after stimulation with alcohol or histamine The term combined acid has no clinical significance (It is the opinion of most authorities that the latter expression should be discarded)(211)

TECHNICAL NOTES *Phenolphthalein tests for the total acidity while Topfer s reagent tests for free hydrochloric acid* The results are inaccurate if bile is present in the specimen Stimulation may be produced by histamine subcutaneously by 50 ml of 7 per cent ethyl alcohol intragastrically or by the injection of 15 to 25 units of regular insulin

The tubeless method consisting of the oral ingestion of a quininium resin indi

cator (Diagnex) and subsequent assay of the urine, holds clinical promise The quinine released by the hydrochloric acid is absorbed and measured in the 2 or 3 hour urine specimen (185, 202, 210) With the substitution of the blue dye, azure-A, for the quinine, the presence of free acid results in the patient s urine turning blue or blue-green within 2 or 3 hours

The accuracy of the tubeless methods for determining gastric acidity is interfered with by pyloric obstruction, impairment of small intestinal absorption, disease of the liver, and impaired renal function (185)

CLINICAL CLUES The presence or absence of free hydrochloric acid should be routinely determined in gastric carcinoma, pernicious anemia sprue, and combined system disease suspects The "ab ence of free acid" in cases of benign peptic ulcer is usually the result of the tube being placed in the proximal part of the stomach It can also be due to large amounts of buffering mucus or serum oozing from the ulcer This prevents a drop in the pH below 4 0 or 4 5 and the development of a red color when Topfer s reagent is added

Blood (Including the String Test)

NORMAL RANGE None

TECHNICAL NOTES Benzidine and other tests for blood are added to the gastric secretions The string test is generally unreliable in bleeding from the lower stomach or duodenum This technique may be made more accurate by rendering the distal 12 inches radio-opaque and determining its position by fluoroscopy prior to removal (208)

CLINICAL CLUES Significant bleeding may be caused by gastritis ulcer cancer hiatal hernia, esophageal varices and blood vessel erosion (pp 493 to 499) "Coffee-ground vomitus is usually indicative of prolonged retention of blood within the stomach which leads in turn to the formation of acid hematin

Microscopic

NORMAL RANGE No food particles

TECHNICAL NOTES Also see Exfoliative Cytology (p 791)

CLINICAL CLUES The presence of many undigested food particles and bacteria indicates stasis

Uropepsin

NORMAL RANGE At least 1500 units in the urine are excreted per diem (average 2350 units per diem) This represents a measure of pepsin production by the peptic glands (One unit is that amount which during 30 minutes of incubation at 37° C in the standard assay releases 0 04 mg of tyrosine-like substance)

TECHNICAL NOTES A modification of the method by Bucher Mirsky, and Anson on aliquots of 24-hour urine specimens is employed

CLINICAL CLUES Levels averaging 6700 units per diem occur in active duodenal ulcer They are also elevated in benign gastric ulcer, even when little free hydrochloric acid is present in the stomach This technique might prove to be a good screening test for gastric atrophy in suspected gastric carcinoma or pernicious anemia (The blood pepsin assay may also later prove to be helpful in the diagnosis of gastric-duodenal disease)(212)

The marked variation in the daily excretion of urinary uropepsin along with the marked overlapping between the values that are set forth as normal and those encountered in many gastrointestinal diseases renders this test of little practical value in differential diagnosis (192b)

Soda Water Test for Pyloric Obstruction (see Section XVI, p 830)

DUODENAL SECRETIONS, PANCREATIC AND INTESTINAL FUNCTION (178 183, 201)

Pancreatic Drainage

Technical Notes These studies are usually performed only by investigators especially interested in this field A minimal amount of gastric juice should be present in the secretions A double lumen gastroduodenal tube is passed to the ligament of Treitz The blood levels of pancreatic enzymes are usually more reliable

Clinical Clues Duodenal drainage may on occasion be helpful in the diagnosis of chronic pancreatitis and carcinoma of the pancreas both of which can produce baffling symptom complexes (pp 47 and 328) Perhaps the most characteristic feature of pancreatic insufficiency with the secretin test is the finding of a bicarbonate concentration less than 90 mEq /L The results may be normal however in pancreatic tumors which involve only the tail of the gland

VOLUME

Normal Range 135 to 250 ml per hour

pH

Normal Range 5 5 to 7 5

BICARBONATE

Normal Range 90 to 130 mEq per hour

AMYLASE

Normal Range 300 to 1200 Russell units per hour

SODIUM

Normal Range 140 mEq per liter

LIPASE

Normal Range 7000 to 14 000 units per hour

TRYPSIN

Normal Range 20 to 40 units per hour or the digestion of gelatin in a 1 to 50 dilution or higher (Values from 35 to 160 per cent may be normal in the absence of pancreatic disease)

Biliary Fluid

Normal Range Bile from the common hepatic and cystic ducts is light in color whereas bile from the gallbladder is dark Cholesterol crystals may be

present (A polarizing filter and the yellow staining with sulfuric acid can aid in identifying true cholesterol crystals)

TECHNICAL NOTES The sphincter of Oddi can be relaxed by injecting 50 ml of 25 per cent magnesium sulfate into the tube Bile from the gallbladder is collected more readily after 15 to 30 ml of olive oil and hot water are introduced Cytology is discussed in the section on "Exfoliative Cytology" (p 791)

CLINICAL CLUES The finding of amorphous calcium bilirubinate and cholesterol crystals in the presence of jaundice is suggestive of biliary calculi The procedure may also be therapeutic by causing a stone in the distal common bile duct to pass Caution must be used in interpreting the results, since biliary crystals can occur in noncalculous pancreatic, hepatobiliary and hemolytic disease Furthermore, gallstones may still be present in the absence of such crystals

Lipase (Blood)

NORMAL RANGE 0 2 to 1 5 units (ml of sodium hydroxide required to neutralize the fatty acids released by 1 ml of serum)

TECHNICAL NOTES Serum A substrate of olive oil is employed, which is hydrolyzed to fatty acids by enzymes in the serum

CLINICAL CLUES Elevated in pancreatitis, pancreatic neoplasm, after opiate administration (even without pancreatitis) and acute hepatitis (193)

Amylase (Blood)

NORMAL RANGE 60 to 200 Somogyi units (mg of glucose per 100 ml of serum)

TECHNICAL NOTES Serum Several methods are employed, either relating to the hydrolysis of starch or measuring the starch iodine color

CLINICAL CLUES Elevated in pancreatitis (usually diagnostic *only* if it is increased 4 to 5 times) duodenal ulcer after opiate administration, peritonitis acute renal insufficiency (T–176) acute small bowel obstruction (T–1374) uremia and inflammation of the salivary glands (193)

Secretin Test and Methacholine (Mecholyl) Test (182)

NORMAL RANGE A moderate rise in both the blood enzymes and in the pancreatic juice volume and bicarbonate is normally produced The juice is richer in bicarbonate following secretin and richer in enzymes following methacholine

TECHNICAL NOTES Purified secretin is given intravenously (1 unit per kg of body weight) The methacholine bromide (Mecholyl) dose is 10 to 15 mg subcutaneously The blood levels of lipase and amylase are followed When facilities are available the gastric and duodenal drainages may be studied using a double lumen gastroduodenal tube

CLINICAL CLUES In atrophy of the pancreas no hyperenzymemia ensues In pancreatic obstruction marked rises may occur The test is expensive, usually not diagnostic, and generally not very reliable

Starch Tolerance Test (175)

NORMAL RANGE A significantly greater rise in the blood sugar level normally occurs after glucose than after starch ingestion

TECHNICAL NOTES 100 gm of soluble starch is ingested in 450 ml water Blood sugar levels are followed at ½ 1 2 and 3 hours A glucose tolerance test with 100 gm glucose is also performed

CLINICAL CLUES No rise of the blood sugar occurs in chronic pancreatitis after the ingestion of starch (since it cannot be broken down)

D Xylose Absorption Test (177a)

NORMAL RANGE The urinary excretion averages 6 5 ± 1 2 gm in 5 hours in healthy subjects A prompt peak occurs in the blood in one or two hours followed by a rapid fall

TECHNICAL NOTES The fasting patient is given 25 gm of d xylose dissolved in 250 ml of tap water The urine is collected over a 5-hour period in one container and refrigerated Oxalated venous blood samples are drawn at ½ 1 1½ 2 3, and 4 hours after the test dose Colorimetric analyses are then done

CLINICAL CLUES This test has been advocated in the diagnosis of the malabsorption syndromes since the pentose d xylose is apparently unaltered by the liver and does not undergo the selective absorption as does glucose Untreated patients with sprue excrete only 1 gm in the urine, and those in remission but slightly more It is normal in pancreatogenous steatorrhea The deficient absorption after partial gastrectomy and small bowel disorders is also manifest by this test The blood values may exhibit considerable overlapping in both patients with sprue and normal individuals, obviating much of the blood test s designed specificity

Serum Lipids and Serum Calcium (see "Blood Chemistries," pp 688 and 684, respectively)

Carotene

NORMAL RANGE 70 to 200 microgm per 100 ml (Most normal individuals fall within the narrower range of 100 to 180 microgm per 100 ml) The level is influenced by diet liver disease and febrile states

TECHNICAL NOTES Plasma Readily performed with the colorimeter

CLINICAL CLUES *This test has proved to be one of the most reliable* screening guides in the diagnosis of the malabsorptive syndromes and in differentiating sprue from functional diarrhea (T-152) Levels of 30 to 70 microgm per 100 ml indicate moderate depletion this can be readily elevated if due solely to dietary factors Levels of 0 to 30 microgm per 100 ml indicate severe depletion of this fat-soluble vitamin and are found in steatorrhea they may rise following successful therapy Elevated levels occur in the hyperlipemias nephrosis diabetes mellitus hypothyroidism and after the excessive ingestion of carrots (taken in an attempt to improve vision)

Plasma Antithrombin Titer (198)

NORMAL RANGE 1 to 6 antithrombin units with clotting occurring within a prescribed range at 1 5 10 and 15-minute incubation periods

TECHNICAL NOTES A modification of the method of Quick Strict attention to the details of the test are important A unit of antithrombin is defined as that amount present in a 2 ml aliquot of plasma which, when added to 1/10 ml of standardized thrombin forms a clot in 15 seconds

CLINICAL CLUES This test is considered positive if a minimum of twenty antithrombin units are demonstrable not later than the 15-minute incubation period It could be helpful as a supplementary test in acute pancreatitis and chronic relapsing pancreatitis where the amylase values are found to be borderline High titers may persist for 36 to 48 hours Morphine does not provoke elevated titers

The Finger-Imprint Chloride Test (T-165c)

NORMAL RANGE The majority of healthy children and sick children who do not have cystic fibrosis of the pancreas will yield a + reaction (the reactions being rated as +, ++, and +++) This corresponds to a concentration of 60 mEq /L or less

TECHNICAL NOTES A finger or hand imprint (or in small infants, a toe or foot impression) is made with light pressure on a medium composed of silver nitrate and potassium chromate suspended in an agar base If considerable chloride is present on the surface of the skin, there will be an immediate and intense whitish yellowish discoloration A standard solution of 100 or 150 mEq /L of sodium chloride may be used for comparison One should also take into account such factors as unilateral muscular, neurogenic or vascular disturbances, the environmental temperature, the diet, the state of the renal and adrenal function, and the presence of fever or dehydration in evaluating the results

CLINICAL CLUES This is a rapid, inexpensive, and painless method for the screening of patients with suspected cystic fibrosis of the pancreas A +++ reaction is almost universally found in these children due to the increased chloride content of their skin If the simple finger imprint chloride method proves positive in a suspected case of cystic fibrosis of the pancreas, it is wise to confirm the diagnosis by either the sweat test (in which the concentration of sodium and chloride in the body sweat are determined), or by a study of the duodenal fluid A +++ reaction among the siblings of these patients may be of great aid in identifying unrecognized cases of cystic fibrosis (p 48)

X RAY STUDIES (188)

Stomach, Esophagus and Duodenum

NORMAL RANGE Normal configuration tone, and position No gastric residue should be present after 3 hours

TECHNICAL NOTES Careful fluoroscopy with thick and thin barium mixtures is necessary The patient should be examined in all positions Spot films of the duodenal cap should be routinely obtained The test should be repeated every 6 to 12 months in patients with pernicious anemia and in those with previously removed gastric polyps but with the least amount of radiation It should also be performed in refractory anemias to rule out blood loss from a hiatal hernia or a chronic ulcer (T-1007)

When x rays of the stomach are taken shortly after a bout of massive gastrointestinal bleeding it is important to evacuate the stomach of both secretions and blood clots with a stomach tube of wide diameter and subsequent lavage (using either ice water or lukewarm water) prior to x ray Emergency x ray study of the patient with gastrointestinal hemorrhage should not be attempted in patients who are vomiting or on the brink of shock

The long term complications of radiation pose a definite calculated risk to patients who are subjected to repeated studies of the gastrointestinal tract (p 395)

Nelson has reviewed several important factors which must be borne in mind if one is to obtain the highest positive yield of demonstrable esophageal and gastric varices by x ray (204) In this regard the value of the recumbent and Trendelenburg positions, the use of thick barium mixtures after a previous injection of atropine and the use of both the Valsalva and Muller maneuvers are noteworthy

CLINICAL CLUES A number of systemic illnesses should be considered (Addison's disease, porphyria, hemochromatosis sickle cell disease etc) if these

studies are repeatedly negative in the presence of long standing abdominal complaints (p 491)

Esophageal changes may be noted in scleroderma A benign tumor especially a leiomyoma, should be suspected if mucosal rugae persist in the area of an esophageal neoplasm

Attention may be directed to the presence of a poorly visualized, flat infiltrating carcinoma of the cardia by the jetlike stream or the delay at the cardia noted on fluoroscopy with the first few swallows of barium With experience it is possible to demonstrate tumors as small as 5 mm in diameter

In the presence of marked spasm and deformity it may be difficult to distinguish a duodenal ulcer from a gastric ulcer The recurrence of multiple stomach duodenal jejunal, or stomal ulcers in spite of extensive surgery and intensive medical management suggests the Zollinger Ellison syndrome (p 20) (T-53)

Wolf and Marshak have stressed three profile features whose association with a niche suggests the presence of a benign gastric ulcer (215) These include the following (1) the Hampton line consisting of a thin lucent line with parallel straight margins which crosses the orifice of the niche This line apparently represents the undermined mucosal edge that surrounds the crater It is almost pathognomonic of a benign lesion (2) The ulcer collar which is more common and is observed as a lucent band that is noted between the general lumen of the stomach and the niche This sign appears to represent the limited distensibility of the gastric wall adjacent to the niche It bears some relationship to the size of the ulcer crater (3) The ulcer mound representing the induration of the gastric wall for some distance beyond the crater Even so, there may be considerable difficulty encountered in differentiating certain of these halos around benign gastric ulcers from the marginal ridge of an ulcerated carcinoma

Giant hypertrophy of the gastric rugae(T-1149) bezoars(T-1150), hyperplasia of the Brunner s glands and aberrant pancreatic tissue or localized hyperplasia of the lymphoid follicles involving the duodenum(T-1151 1153) have all produced misleading x ray patterns Changes in the motor function and mucosal pattern of the duodenum and stomach occur earlier in carcinoma of the pancreas than do widening of the duodenal loop or the inverted-3 sign (T-1041 1042) One should be very skeptical about the interpretation or significance of prolapse of the gastric mucosa into the duodenum (T-1345)

Small Intestine (191, 197) (T 153e)

NORMAL RANGE Normal appearance without significant ' puddling Most of the barium should have left the ileum after 8 hours

TECHNICAL NOTES Films are taken at 30- or 60-minute intervals after the routine barium swallow or more rapidly if iced saline is used as the barium vehicle (Many radiologists avoid the use of both saline and ice water because they can produce disturbances in the small intestinal pattern *per se*) Large quantities of barium should be ingested when either the sprue syndrome or diffuse lesions of the small intestine are suspected so that many intestinal loops can be simultaneously visualized

There are many modifications of the small bowel enema These primarily consist in the visualization of the small intestine following the introduction of dilute barium into a Rehfuss tube placed in the duodenum

When there is a suspected obstruction of the small intestine which would render the ingestion of barium sulfate preparations hazardous preliminary studies can be made with safety by the use of the water soluble contrast media that are employed for intravenous urography or angiocardiography (T-1363) These substances

might also be much safer in the examination of the large bowel when such considerations as intussusception or possible perforation of the intestine arise

The reader is also referred to the discussion (pp 499–508) of x ray findings in patients with bowel obstruction in the text

CLINICAL CLUES This study should be performed in the presence of unexplained bleeding colic, spotty melanin pigmentation, and steatorrhea for the various inflammations, degenerations and tumors of the small bowel

The moulage sign" is characteristic of sprue Other features of the "sprue pattern" consist of dilatation, segmentation, fragmentation and scattering of the barium column, thickening of the mucosal folds, hypersecretion, and motility changes They may also be observed in cases of secondary sprue, such as lymphosarcoma and Whipple s disease but only if marked steatorrhea and increased fatty acids in the stools are present (It is stressed that the individual components of the minimal sprue pattern by themselves are not diagnostic)

The small bowel appears essentially normal in pancreatogenous steatorrhea A spruelike pattern can also be observed after gastric resection, but is infrequently noted in regional enteritis Even in the face of clinical improvement of sprue due to therapy, there is usually little change in the appearance of the small bowel

The following points are offered as clues in the diagnosis of lesions affecting the small bowel

Carcinomas are usually encountered in the jejunum as short single lesions, possibly with overhanging margins or an extraluminal mass

Infarction of the small bowel results in progressive changes and the ultimate development of a stricture with smooth margins and dilatation of the proximal small bowel

Carcinoids most often are observed in the distal ileum and resemble carcinomas radiographically Infrequently they produce the appearance of multiple nodular filling defects

Multiple polyposis of the small bowel is infrequent, it is usually associated with the Peutz Jeghers syndrome

Lymphosarcoma can present as large extraluminal masses with extrinsic pressure on the small bowel a sprue like pattern a polypoid form with intussusception an infiltrating form multiple small nodular defects a large excavated mass having multiple fistulas and communications with the adjacent small bowel (T–635)

Hodgkin s disease can similarly result in the sprue pattern, small nodular defects and infiltrating forms It differs from lymphosarcoma in its tendency to cause fibrosis of the bowel wall and luminal constriction

Regional enteritis produces relatively long (6 to 8 inches) inflammatory segments of the small bowel Two thirds of the cases involve the distal ileum The manifestations may be legion including fistulas sinus tracts spasm hypersecretion skip areas ulcerations and inflammatory polyp formation

Large Bowel (186, 214)

NORMAL RANGE Normal filling configuration, and tone before and after evacuation The terminal ileum appears normal (if visualized)

TECHNICAL NOTES This test should be performed routinely (every 6 months if possible) in patients with chronic ulcerative colitis and with previously removed polyps (T–1008) Here again, however one is confronted with the long term complications of repeated radiation

Only small amounts of tannic acid should be used in order to prevent excessive cramps The cecum and ileocecal valve should be completely visualized (194) A barium enema may be done safely even in the presence of suspected obstruction (See the discussion in Part I dealing with obstruction pp 499 to 501)

The many considerations attendant upon the demonstration of polyps in the colon have been set forth by Robinson (187c) The double contrast technique can be employed to advantage if polyps are suspected (187) Compressed carbon dioxide is being employed in some centers for obtaining double contrast studies of the colon. This procedure is not only more comfortable, but also considerably safer than air since the gas is absorbed quickly and since gas embolism is not a hazard (187b)

Castor oil should not be given to patient with chronic ulcerative colitis in preparation for barium studies since the disease may be reactivated Due to the danger of perforation double contrast studies are generally contraindicated in the presence of acute ulcerative colitis acute diverticulitis or suspected acute appendicitis

Barium studies may help in the selection of other roentgen procedures for the study of suspected retroperitoneal tumors primarily by indicating the size and relative location of the mass The use of the lateral view in these contrast studies is often quite helpful (See paper by Lowman and Davis)(338)

CLINICAL CLUES Radiography is obviou ly very important in the diagnosis and follow up of large bowel lesions It may also be helpful in the diagnosis of ileocolitis, regional ileitis, and amebiasis (190) An appendiceal stump should not be confused with carcinoma of the cecum (T-1148) With experience it is possible to demonstrate tumors 5 mm in diameter Massive hemorrhage from diverticulitis should be diagnosed *only* by exclusion (T-1138)

Loss of haustrations is *not* sufficient evidence for a diagno is of early ulcerative colitis Thickening of the mucosa and multiple tiny serrations along the edges of the bowel are more reliable guides (199) In relatively mild cases of ulcerative colitis the only x ray finding may be that of a decreased distensibility of the rectal ampulla The barium enema is *not* a reliable method for diagnosing diseases of the rectum

Competent radiologists have pointed out the difficulties in identifying (1) acute episodes of diverticulitis in the presence of marked induration due to a chronic diverticulitis (2) an underlying or coincident chronic process when associated with a new acute episode and marked spasm and (3) small residual deformities from previous acute attacks in the presence of a deformed and shortened bowel Probably the most useful way of differentiating diverticulitis from carcinoma is the demonstration that the deformities or defects of the former are covered by intact mucosa (216)

It is stressed that a normal appearance of both the colon and the terminal ileum by barium enema studies does *not* exclude the diagnosis of regional enteritis (T-168b)

Gallbladder Visualization

TELEPAQUE

NORMAL RANGE Normal filling and concentration significant contraction following a fatty meal

TECHNICAL NOTES 4 to 6 (or more) Telepaque tablets should be administered the evening before and the patient warned about the possible ensuing cramps or mild diarrhea After the initial films are taken a fatty meal or Neo-cholex is given to observe gallbladder contraction

This study is inaccurate in the presence of either gross icterus (i e a total serum bilirubin exceeding 5 mg per 100 ml) or a BSP retention of more than 20 per cent at 45 minutes (184) This test should be withheld if I^{131} or protein bound iodine

studies are anticipated It is also preferable not to perform a BSP test within several days of a gallbladder study

CLINICAL CLUES A wide variation of normal gallbladder patterns exists The test is 95 per cent accurate for gallbladder function and disease A normal gallbladder may not be visualized, however, for several weeks after a bout of acute pancreatitis The period of impaired gallbladder function following an attack of peritonitis of nonpancreatic origin can also be very prolonged (even more than three months) (203) Intravenous cholecystography might be of value under these two circumstances

If one is still clinically in doubt concerning a *nonfilling gallbladder, the test* should be repeated with the same or doubled dose The implications of a "non functioning gallbladder may be misleading if the possibility of improper absorption of the contrast medium is not entertained as for example in the case of an esophageal diverticulum or cardio pasm (195b)

CHOLOGRAFIN (SODIUM IODIPAMIDE) (179)

NORMAL RANGE A common duct diameter measurement of less than 8 mm and complete clearing of the medium within 120 minutes indicates an unobstructed duct

TECHNICAL NOTES 40 ml of the 20 per cent solution are injected intravenously preceded by the intravenous administration of 20 mg Benadryl The patient is observed for 1 to 2 minutes after the first ml has been injected before giving the remainder Films are taken every 10 to 15 minutes for 2 hours with the patient in the supine position and the left side elevated 15 degrees Visualization does not usually occur when the serum bilirubin exceeds 5 0 mg per 100 ml, or when the BSP retention exceeds 60 per cent

CLINICAL CLUES Whereas the visualization of the gallbladder by oral cholecystography is dependent upon a functioning gallbladder, its visualization by intravenous sodium iodipamide is independent of its functional status This technique has already proved to be of great value in demonstrating partial obstruction of the common duct in the postcholecystectomy syndromes, (pp 485 and 486) (T-1323) and as a preoperative supplement to oral cholecystography when the gallbladder fails to visualize

A duct diameter greater than 15 mm indicates obstruction Since dilated ducts may be found after cholecystectomy in certain patients who are asymptomatic and exhibit no evident obstruction, the time-density factor might be important in correctly interpreting the results By comparing the density of the contrast medium in the duct at 120 minutes with that at 60 minutes partial obstruction can be inferred if no decrease is observed in the degree of density

Intravenous cholangiography may prove to be of great value in the early diagnosis of cancer involving the head of the pancreas This stems from the intimate relationship between this organ and the common bile duct (T-1041d)

RADIOGRAPHY WITHOUT GALLBLADDER CONTRAST MEDIUM

TECHNICAL NOTES Spot films of the gallbladder area are taken in various positions Laminograms may infrequently prove to be of some help

Right lateral films are occasionally of considerable aid in differentiating calcification in the kidney from that within the gallbladder One can infer that a gall stone is fixed when the lower pole of the stone points medially (T-1362c) It is possible that laminography might demonstrate the presence of gallstones when the routine cholecystograms have failed to do so (195a)

Pyelography for Lesions of the Pancreas (181)

TECHNICAL NOTES Films taken with the patient in the supine position following intravenous pyelography are studied Particular attention is directed to the configuration of the left kidney

CLINICAL CLUES Significant pressure effects may be exerted upon the left kidney by tumors involving the body or tail of the pancreas

Abdominal Aortography (Liver and Spleen) (209)

TECHNICAL NOTES A size 16 needle is introduced medially and cephalad just below the eleventh rib into the aorta 40 ml of 35 per cent or 70 per cent Urokon are injected within 3 seconds Films should be taken as rapidly as possible preferably at 1 second intervals using the Fairchild cassette A good visualization of the entire portal venous system occurs in 8 to 12 seconds Injection of the contrast medium has also been done through the spleen and directly into the portal vein (186)

CLINICAL CLUES This procedure is obviously highly specialized but may be used to good advantage in the presence of suspected abnormality of the extrahepatic portal circulation and with suspected liver tumors The frequent coagulation disturbance in cirrhosis makes it undesirable in this disease The greatest value of percutaneous splenoportography is in the preoperative localization of portal obstruction (viz, whether intrahepatic or extrahepatic) and in assessing the patency of a previous portacaval shunt

Diagnostic Pneumoperitoneum (see Section XII, p 803)

ENDOSCOPY

Sigmoidoscopy

NORMAL RANGE Normal appearance of the anus rectum and rectosigmoid

TECHNICAL NOTES This very important procedure is facilitated by the patient s being well prepared and reassured and by using the knee-chest or Sims positions A warm sigmoidoscope should be used It should routinely precede a barium enema this maneuver also allows for some air contrast in the films of the large bowel

CLINICAL CLUES Sigmoidoscopy should be a routine part of the complete gastrointestinal study This is particularly true if anemia is present or if polyps were previously found It may also be diagnostic of ulcerative colitis and amebiasis

Gastroscopy (205)

NORMAL RANGE Normal appearance of the gastric mucosa with good visualization of the area high up on the greater curvature

TECHNICAL NOTES A flexible or adjustable mirror gastroscope is introduced after local anesthesia and parenteral sedation (preferably with meperidine) have been given The examination should be stopped if a marked local pathologic condition is present in the cervical spine aorta or esophagus or if one is unable to pass the instrument readily (207)

CLINICAL CLUES This examination may occasionally be a useful supplement to x rays in diagnosing acute or chronic gastritis (T-1330) gastric carcinoma benign ulcer gastric polyps and varices in the esophagus or stomach

studies are anticipated It is also preferable not to perform a BSP test within several days of a gallbladder study

CLINICAL CLUES A wide variation of normal gallbladder patterns exists The test is 95 per cent accurate for gallbladder function and disease A normal gallbladder may not be visualized, however, for several weeks after a bout of acute pancreatitis The period of impaired gallbladder function following an attack of peritonitis of nonpancreatic origin can also be very prolonged (even more than three months) (203) Intravenous cholecystography might be of value under these two circumstances

If one is still clinically in doubt concerning a nonfilling gallbladder, the test should be repeated with the same or doubled dose The implications of a "non functioning gallbladder may be misleading if the possibility of improper absorption of the contrast medium is not entertained, as for example in the case of an esophageal diverticulum or cardiospasm (195b)

CHOLOGRAFIN (SODIUM IODIPAMIDE) (179)

NORMAL RANGE A common duct diameter measurement of less than 8 mm and complete clearing of the medium within 120 minutes indicates an unobstructed duct

TECHNICAL NOTES 40 ml of the 20 per cent solution are injected intravenously preceded by the intravenous administration of 20 mg Benadryl The patient is observed for 1 to 2 minutes after the first ml has been injected before giving the remainder Films are taken every 10 to 15 minutes for 2 hours with the patient in the supine position and the left side elevated 15 degrees Visualization does not usually occur when the serum bilirubin exceeds 5 0 mg per 100 ml or when the BSP retention exceeds 60 per cent

CLINICAL CLUES Whereas the visualization of the gallbladder by oral cholecystography is dependent upon a functioning gallbladder its visualization by intravenous sodium iodipamide is independent of its functional status This technique has already proved to be of great value in demonstrating partial obstruction of the common duct in the postcholecystectomy syndromes (pp 485 and 486), (T-1323) and as a preoperative supplement to oral cholecystography when the gallbladder fails to visualize

A duct diameter greater than 15 mm indicates obstruction Since dilated ducts may be found after cholecystectomy in certain patients who are asymptomatic and exhibit no evident obstruction the time-density factor might be important in correctly interpreting the results By comparing the density of the contrast medium in the duct at 120 minutes with that at 60 minutes partial obstruction can be inferred if no decrease is observed in the degree of density

Intravenous cholangiography may prove to be of great value in the early diagnosis of cancer involving the head of the pancreas This stems from the intimate relationship between this organ and the common bile duct (T-1041d)

RADIOGRAPHY WITHOUT GALLBLADDER CONTRAST MEDIUM

TECHNICAL NOTES Spot films of the gallbladder area are taken in various positions Laminograms may infrequently prove to be of some help

Right lateral films are occasionally of considerable aid in differentiating calcification in the kidney from that within the gallbladder One can infer that a gall stone is fixed when the lower pole of the stone points medially (T-1362c) It is possible that laminography might demonstrate the presence of gallstones when the routine cholecystograms have failed to do so (195a)

TECHNICAL NOTES A fresh smear of the fecal emulsion is most valuable particularly in amebiasis Concentration techniques by either the centrifuge or flotation methods may be employed The physician *himself* should always check doubtful smears

CLINICAL CLUES This examination constitutes an indispensible part of the study of suspected parasitic disease caused by roundworms flatworms, intestinal protozoa and flagellates

WHITE BLOOD CELLS AND EPITHELIAL CELLS

NORMAL RANGE Present in occasional numbers

TECHNICAL NOTES Verified by examination of a saline suspension or a stained smear of the stool

CLINICAL CLUES In uncomplicated cases of amebic dysentery the exudate consists mostly of mucus and red cells In bacillary dysentery and in ulcerative colitis many pus and blood cells are intimately mixed Eosinophilia of the stool could suggest an allergic condition

UNDIGESTED MEAT FIBERS

NORMAL RANGE Infrequently noted in the absence of diarrhea

TECHNICAL NOTES The patient should be placed on a diet containing large amounts of chopped beef or ham either given raw or lightly broiled Observe for yellow muscle fibers with square ends sharp edges and well preserved striations in the stool

CLINICAL CLUES A good simple test for the proteolytic functions of the pancreas Undigested meat fibers may not be found in pancreatic insufficiency if the fecal material remains in the bowel a long time (due to the action of proteolytic bacteria)

Fat

NORMAL RANGE Not normally found

TECHNICAL NOTES The stool should be properly treated with 30 per cent acetic acid and heat before the sudanophilic stain is added since the fatty acids pick up the dye indifferently even though the neutral fats stain well Neutral fat appears as yellowish flakes or droplets fatty acids as flakes or needle-like crystals and soaps as amorphous flakes or rounded masses as well as needle like crystal

CLINICAL CLUES The loss of fat in the stool may be prominent in cases of chronic pancreatitis and steatorrhea

Fat (Quantitative)

NORMAL RANGE Less than 5 gm in 24 hours (or less than 4 per cent of the fat intake) is excreted over a 3 day period while on a Schmidt diet (105 gm protein 135 gm fat and 180 gm carbohydrate) The timing is determined with a carmine marker given at the first meal and with charcoal ingested on the fourth day

TECHNICAL NOTES A 24-hour or 3-day specimen preserved in 95 per cent alcohol is studied This test is technically demanding and expensive and is used primarily in investigation

CLINICAL CLUES The presence of more than 10 per cent of the ingested fat—or of 30 per cent of the total dry stool in fat—with over 75 per cent of it

Esophagoscopy (213)

NORMAL RANGE Normal appearance of the esophagus

TECHNICAL NOTES Introduction of the optical esophagoscope with a flexible obturator (Eder Hufford) and a four-diameter magnification lens is a safe procedure in experienced hands Biopsies can be taken with relative ease

CLINICAL CLUES Very valuable as a supplement to fluoroscopy and x rays in diagnosing diseases of the esophagus The latter include in particular esophageal varices in the presence of unexplained gastrointestinal hemorrhage esophagitis and gastritis occurring within hernial pouches (180)(T-1335 1337) It is less helpful in lesions lying above the arch of the aorta The linear mucosal tear of the Mallory Weiss syndrome may not be visualized by x ray, but might be seen by esophagoscopy

STOOL EXAMINATION

Blood

NORMAL RANGE Should be absent particularly if the patient has been on a meat free diet

TECHNICAL NOTES The sensitivity of the various tests increases from the guaiac to the benzidine dihydrochloride to the orthotolidine reagents respectively It is best to examine the stool from the center for blood

Most individuals who ingest ferrous sulfate actually have negative guaiac tests on their stools It is possible that the positive tests which occur represent the lack of change of this drug in the gastrointestinal tract due to altered motility or digestion One can differentiate a positive guaiac test caused by iron or blood by extracting with ether the iron being present in the ether layer

The black stool in gastrointestinal bleeding is produced by the formation of acid hematin This occurs either as a result of the digestion of hemoglobin by gastric acid or by the production of the sulfide of heme due to the action of hydrogen sulfide on the iron component of heme (T-1329b)

CLINICAL CLUES This test must be frequently repeated to exclude blood loss as a cause of obscure anemia, particularly from a hiatal hernia (T-1333) The guaiac test may be positive with as little as 3 ml blood on an unrestricted diet or with 20 ml on a meat-free diet There must be at least 50 ml of blood for the development of a black stool

If bowel bleeding occurs in a patient receiving anticoagulants, one ought to rule out an underlying gastrointestinal malignancy (T-1026) Significant bleeding should be attributed to diverticulitis *only* by exclusion (T-1338) The various causes of gastrointestinal bleeding are discussed in Part I, (pp 493 to 499)

Trypsin

NORMAL RANGE The gelatin layer of an x ray film is liquefied if trypsin is present

TECHNICAL NOTES A simple test based on the liquefaction of gelatin on an x ray film It is of value primarily in infancy

CLINICAL CLUES Liquefaction is absent in pancreatic deficiency and in fibrocystic disease of the pancreas Gelatinases can be produced by bacteria in the normal stool, however and may give false results

Microscopic

PARASITES AND OVA

NORMAL RANGE Pathogens are absent

Technical Notes A fresh smear of the fecal emulsion is most valuable particularly in amebiasis Concentration techniques by either the centrifuge or flotation methods may be employed The physician *himself* should always check doubtful smears

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Clinical Clues The presence of more than 10 per cent of the ingested fat—or of 30 per cent of the total dry stool in fat—with over 75 per cent of it

being hydrolyzed (to soaps and free fatty acids), indicates a significant steatorrhea (pp 44–49) (178 201)

Nitrogen (Quantitative)

NORMAL RANGE Less than 2 gm in 24 hours or 10 per cent of the urinary nitrogen is excreted

TECHNICAL NOTES A 24 hour or 3-day specimen is studied

CLINICAL CLUES Marked loss occurs in pancreatogenous creatorrhea (178, 210)

Urobilinogen (Quantitative) (see Section IV, p 718)

GASTROINTESTINAL CYTOLOGY

(See Section X ' Exfoliative Cytology ' p 79)

OTHER PROCEDURES

Intestinal Absorption of Co^{60} B_{12} of High Specific Activity (18, 32, 189)

TECHNICAL NOTES Absorption may be measured in several ways

(1) measurement of the fecal excretion of radioactivity following an oral dose

(2) measurement of the urinary excretion of radioactivity following an oral dose before and after intravenous nonradioactive B_{12}

(3) measurement of the hepatic uptake following the tracer dose (with the scintillation counter being directed perpendicular to the liver) the abdominal counts are used as controls One can take counts over the liver as early as 48 hours after the administration of the tracer dose of radioactive B_{12} by removing the unabsorbed material with a cathartic and enema (18)

The various advantages and drawbacks of these methods have been reviewed by Glass (18)

CLINICAL CLUES A complete block to the intestinal absorption of vitamin B_{12} exists in pernicious anemia (both in relapse and in remission), after total gastrectomy, and in sprue The mean urinary excretion in normal individuals is 13 3 per cent In patients with pernicious anemia, it is 0 85 per cent This technique is still experimental, but it may assume diagnostic importance in the differentiation of the macrocytic nutritional and malabsorption anemias in the early diagnosis of sprue and in disturbed secretory activity of the gastric glands Impaired absorption of B_{12} also occurs in patients with diabetes mellitus especially when there is a complicating retinopathy or neuropathy (T–260b)

Radioactive Chromium Studies (44)

TECHNICAL NOTES One unit of Cr^{51} labeled red blood cells is infused into the bleeding patient The blood volume can be readily determined The presence of any radioactivity is also checked in the stools that are subsequently passed

CLINICAL CLUES This is a very accurate method of determining the blood volume and the need for further transfusions in the patient who has lost blood It can also conclusively demonstrate the existence or cessation of active gastrointestinal bleeding when tarry stools persist

Peritoneoscopy (176)

TECHNICAL NOTES The peritoneoscope (Ruddock and other types) is used under general anesthesia preferably with sodium pentothal Intestinal distention is an absolute contraindication The relative contraindications include acute inflammatory processes the presence of marked adhesions diminished respiratory capacity debility and a low prothrombin time The diagnostic accuracy is enhanced by the study of tissue biopsied during the procedure

CLINICAL CLUES This technique is most accurate (94 per cent) in benign or malignant diseases of the peritoneal cavity It is progressively less valuable in liver disease gynecologic lesions ascites of undetermined origin, and retroperitoneal tumors (50 per cent accurate) respectively Polycystic disease of the liver has also been readily diagnosed by this method (T-1248 1249)

The Diagnostic Peritoneal Tap (206)

TECHNICAL NOTES After local procaine infiltration a 2-inch short-bevel, 18 to 20 gauge spinal needle is inserted at a right angle near but not directly into the site of the suspected disease Care is taken to avoid the solid organs and the inferior epigastric vessels Gentle suction is applied when the needle is felt to pass into the peritoneal cavity Even when no fluid appears to enter the syringe the needle should be emptied onto a clean glass slide A fresh smear a gram stain and a Wright s stain are performed after a careful gross study of the fluid

CLINICAL CLUES While there can be no doubt that the need for such a study should be infrequent as a determinant for laparotomy and that it is no substitute for considered clinical and surgical judgment it may on occasion be helpful The fluid assumes the following features in the presence of certain disorders

1 Perforated stomach or duodenum—turbid yellow green or brown increased amylase many polymorphonuclear leukocytes on the smear possibly food particles

2 Intestinal strangulation—early the fluid is serosanguinous later it is grossly bloody foul and contains many leukocytes and bacteria

3 Appendicitis—a milky yellow fluid with many leukocytes when perforation has occurred the appearance resembles that of pus with many bacteria being present

4 Intraperitoneal hemorrhage—the fluid resembles whole blood

5 Acute pancreatitis—serosanguinous or a turbid yellow high elevation of amylase activity

The appearance of the fluid in tuberculous peritonitis acute rheumatic fever ascites and carcinomatosis may also be helpful Consult Part I for discussions of pseudomyxoma peritonei (p 345) and peritoneal mesothelioma (p 346)

SECTION VIII

Studies of the Central Nervous System

CEREBROSPINAL FLUID

General Comment

TECHNICAL NOTES A spinal puncture must be performed with caution if a markedly elevated pressure in the cranium is suspected or in the presence of a severe neurosis

CLINICAL CLUES For accurate diagnosis in suspected or undiagnosed diseases of the central nervous system and meninges this examination is practically mandatory The rapid onset of a diplegia following a lumbar puncture is suspicious of a cord tumor Death occurring shortly after this procedure is usually due to herniation of the brain stem In an attempt to reduce the incidence of postmeningitic subdural effusions the amount of spinal fluid removed in an infant or child with bacterial meningitis probably should not exceed 3 ml (T–467b)

Initial Pressure

NORMAL RANGE 70 to 180 mm of water

TECHNICAL NOTES The patient must be relaxed as much as possible either lying on the side or sitting up Jugular pressure studies should be done *only* if a spinal block is suspected

CLINICAL CLUES Elevated in various inflammations infections and neoplasms affecting the central nervous system The syndrome of spontaneous hypoliquorrhea is described as consisting of headache tinnitus, dizziness aggravation in the erect position and either low absent or negative cerebrospinal fluid pressure (232a)

Cell Count

NORMAL RANGE 0 to 8 lymphocytes or mononuclear cells per cu ml 20 to 30 in infants

TECHNICAL NOTES Sodium citrate is used as an anticoagulant if a clot formation is expected The torula organisms should not be confused with red cells in the presence of a chronic meningitis It is important to be aware of the fact that crenation of red blood cells occurs immediately, whether the blood was present before or is due to a traumatic spinal tap (226)

CLINICAL CLUES Variable increases of neutrophils or lymphocytes in the various infections and inflammations are encountered The diagnosis of meningitis and other central nervous system infections is considered in Part I (pp 132 to 138)

A bloody tap can be ruled out if the blood is uniform, under high pressure does not clot and if the supernatant fluid is xanthochromic While the finding of crenated red cells is of little clinical assistance the presence of "ghost cells (envelops of erythrocytes) and xanthochromia is definitely indicative of preexisting subarachnoid or intraventricular bleeding

The cell count of lymphocytes in poliomyelitis is usually less than 500 per cu ml Lymphocytic choriomeningitis and an ECHO aseptic meningitis should be suspected when more than 650 per cu ml are present (T–473) An eosinophilia of the spinal fluid in the presence of a suggestive brain tumor should raise the possibility of cysticercosis cerebri (p 175) (T-633)

Chloride

Normal Range 120 to 130 mEq per liter or 700 to 750 mg per 100 ml (as sodium chloride) In infants 650 to 720 mg per 100 ml

Technical Notes This level is 20 mEq per liter higher than in the serum It may be reduced by elevated protein levels in the spinal fluid

Clinical Clues Reduced in acute meningitis particularly when tuberculous It may also be helpful in both prognosis and in the differentiation of meningitis from meningeal irritation (222)

Protein

Normal Range Lumbar 15 to 45 mg per 100 ml cisternal 15 to 25 mg per 100 ml , ventricular 5 to 15 mg per 100 ml

Technical Notes A very valuable and important determination Various *chemical physical and immunochemical methods are employed* The Pandy test precipitates both albumin and globulin it is most useful when only a small amount of spinal fluid can be studied 4 mg per 100 ml is subtracted for each 5000 erythrocytes per cu ml present

Clinical Clues Varying elevations of the spinal fluid protein occur in infections, inflammations hemorrhage cord and brain tumors or compression, and rheumatoid spondylitis A marked rise in the absence of cells may occur in the diphtheritic diabetic and infectious types of polyneuritis (T–583 1135 1136)

Glucose

Normal Range 50 to 75 mg per 100 ml in adults 70 to 90 mg per 100 ml in children under ten years

Technical Notes *This level is 20 mg less than in the blood The blood* glucose level is determined for comparison if doubt arises as to the significance of the spinal fluid level The rapid five-test tube semiquantitative method with Benedict s reagent may be used

The glucose level should be determined within two hours to avoid misleadingly low levels caused by glycolysis

Clinical Clues Nearly always reduced in purulent and tuberculous meningitis unless the patient is receiving intravenous fluids with glucose (222) It may also be reduced in the presence of diffuse leptomeningeal tumor metastases (220 227) The level is usually normal in aseptic meningeal reactions

Colloidal Gold

Normal Range 0000000000 to 1110000000

Technical Notes Influenced by relative increases in the globulins The presence of blood will produce false positive reactions

CLINICAL CLUES Zone I is the so called "paretic curve", Zone II is the "tabetic curve" Multiple sclerosis may produce a first-zone curve Meningitis, virus diseases, vascular lesions, and tumors can produce a midzone curve, or a Zone III reaction

Serology

NORMAL RANGE Negative

TECHNICAL NOTES The blood serology should be concomitantly checked Titers are performed before and after therapy for neurosyphilis A T P I test or one of its modifications may also be done when doubt still exists (p 746)

CLINICAL CLUES This determination should never be neglected when dealing with obscure neurologic syndromes (T-552) The blood serology may be negative in up to 10 per cent of tertiary syphilis cases It is well to bear in mind that 14 of 100 patients with neurosyphilis in one series had negative immobilization tests on the spinal fluid (T-555a)

Color

NORMAL RANGE Clear and colorless

TECHNICAL NOTES Xanthochromia occurs when an excess of 0 05 mg bilirubin per 100 ml is present The fluid should also be observed in 24 hours for clot formation

CLINICAL CLUES May be xanthochromic in the presence of an elevated protein (even without any associated bleeding) or in severe regurgitant jaundice Xanthochromia, spontaneous coagulation, and the absence of cells (the Froin syndrome) is very suggestive of cord compression

Complement Fixation Tests

NORMAL RANGE Negative

TECHNICAL NOTES Blood and spinal fluid specimens should be drawn during both the active and convalescent phases of the illness (Also refer to Section VI, pp 740-746)

CLINICAL CLUES Herpes simplex, leptospirosis lymphocytic choriomeningitis, and mumps should be tested for in the presence of benign aseptic meningitis (p 135) (T-473) Other entities are routinely tested for in the 'battery of virus studies that are carried out by the various state and federal laboratories

Bacteriologic Examination

NORMAL RANGE No organisms are present on either smear or culture

TECHNICAL NOTES The gram stain the Ziehl Neelson stain, and various media are employed as indicated (See Infectious Diseases,' p 740) Cultures should also be performed anaerobically Guinea pig infection in the presence of an abacterial purulent meningitis should be routine

CLINICAL CLUES The gram stain and acid fast stain are invaluable in the early diagnosis and treatment of meningitis

Miscellaneous

FAT AND TUMOR CELLS

NORMAL RANGE See 'Urinalysis' (p 709) and Exfoliative Cytology (p 788)

CLINICAL CLUES May be helpful in the diagnosis of cerebral fat embolism and primary or metastatic malignancies respectively (T–481, 792)

TRANSAMINASE

NORMAL RANGE 2 to 7 units per cu ml

TECHNICAL NOTES The indirect spectrophotometric method of Karmen is employed as in the case of the serum determinations

CLINICAL CLUES It has been noted that there is a blood brain barrier in the case of this enzyme Significant and prolonged elevations may be present after cerebral infarction in the absence of any changes in the serum levels and may aid in differentiating this condition from other neurologic disorders (224) On the other hand other investigators have been unable to determine any clear cut diagnostic abnormalities in either the serum or the cerebrospinal fluid transaminase levels in significant numbers of patients with convulsive neoplastic and vascular neurologic disorders studied (224b)

X RAY STUDIES

Skull (223, 231)

TECHNICAL NOTES Proper technique especially the secure immobilization of the head is most important Multiple projections including a film of the base of the skull, and stereoscopic lateral views are usually necessary A systematic study of the general bony structure the sella the base of the skull, the sutures and the individual bones is made The position of the calcified pineal gland and the appearance of the posterior clinoids are often very helpful clues Unilateral calcification of the choroid plexus of the lateral ventricle should not be mistaken for either a markedly shifted pineal gland or a deep seated glioma

CLINICAL CLUES Considerable information relating to both localized and systemic disorders can be obtained from these films including primary and meta static tumors metabolic derangements the reticuloendothelioses Paget s disease, blood dyscrasias and injuries

An increased intracranial pressure must usually be present for 3 months before convolutional atrophy is noted in the skull films Pineal displacement can aid in the diagnosis of an intracerebral hematoma (T–1104) The displacement of the pineal gland is usually away from the tumor but in posterior fossa and cerebellopontine angle tumors with obstruction of the aqueduct the displacement may be posteriorly toward the tumor A similar picture can be produced by occlusion of the vertebral or cerebellar arteries (T–1103)

Calcification may be noted in suprasellar tumors hypoparathyroidism, tuberous sclerosis toxoplasmosis tumors (especially dermoids) torulosis and the Sturge Weber syndrome (219)

Enlargement of the foramen magnum in the presence of cervical and neurologic symptoms suggests an extramedullary tumor at this level (T–1128) Depression of the cribriform plate and enlargement of the internal auditory canal or erosion of the petrous apex may be indicative of frontal and cerebellopontine angle tumors respectively Notching of the clivus has been specifically noted in chordomas which develop at the junction of the sphenoid and occiput (T–109 110)

Ventriculography

TECHNICAL NOTES A cannula is inserted into each lateral ventricle through a trephine opening following which the fluid in the ventricular system is removed

and a lesser amount of air substituted The normal ventricles contain an average of 60 ml fluid The intracranial tension is controlled by manometric pressure readings Multiple films in the various projections are obtained, often with stereoscopic pairs

CLINICAL CLUES This method of pneumography is indicated when a lesion causing blockage of the ventricular pathways and increased intracranial pressure is suspected If performed judiciously and followed by operation shortly after the tumor is located it is considered a safe procedure The block or deformity in the ventricular system may indicate the size, location, and operability of the lesion Its greatest value is in the detection of lesions in the posterior fossa One must remember that air studies may be normal in the presence of brain tumors (T-1106)

Encephalography

TECHNICAL NOTES In this method of pneumography, cerebrospinal fluid is withdrawn and air is injected via the cisternal or lumbar route X rays are taken as in ventriculography Its main disadvantage is that it cannot be safely used in the presence of increased intracranial pressure—particularly when posterior fossa and cerebellar tumors are suspected—due to the danger of herniation of the brain stem through the foramen magnum 80 to 120 cc are injected in adults

CLINICAL CLUES The cortical subarachnoid pathways are diffusely outlined by this means It is consequently of value in localizing such superficial lesions as small cortical tumors, cerebral atrophy, and subdural hematomas It is also of unique help in delineating deep lesions which encroach upon and displace the subarachnoid cisterns, especially in the suprasellar area

Intracranial Angiography (230)

TECHNICAL NOTES The internal carotid artery system is visualized by the use of contrast media and properly timed delayed films These can demonstrate both the arterial and venous networks in the brain The internal carotid arteries supply the major portions of the cerebral hemispheres above the tentorium through their anterior and middle cerebral divisions

Angiography is relatively safe in the presence of increased intracranial pressure This procedure is generally contraindicated, however in the presence of hypertension, severe arteriosclerosis, and recent intracerebral thrombosis or embolism Since multiple intracranial aneurysms may be present over both cerebral hemispheres two injections are often necessary for their lateralizing value

CLINICAL CLUES This technique often offers diagnostic information preoperatively that is not otherwise obtainable It is of unique value in the study of suspected intracranial aneurysms, anomalies of the intracranial vasculature, arterial occlusion, and brain tumors Although an aneurysm may not fill due to the presence of a clot the spasm of adjacent vessels might provide a clue to its presence

Myelography (218)

TECHNICAL NOTES Fluoroscopic visualization and spot films of the distribution of an opaque nonmiscible contrast medium in the subarachnoid space following lumbar puncture is of great value in suspected disorders of the spinal cord Only small amounts (3 to 5 ml) are used but should be withdrawn as completely as possible after the procedure is completed

CLINICAL CLUES The presence and site of a spinal block, intramedullary tumors extramedullary tumors and the rupture of an intervertebral disc may be ascertained by this means (T-1120-1127) Observe for multiple defects at different

levels when a disc is suspected Always check for cervical cord lesions or compression when confronted with unusual degenerative' cord syndromes (T-1125) This technique can also aid in the diagnosis of *epidural granulomas of the spine* (T-1129) and spinal cord extradural hematomas (T-1134) The reader is referred to the discussion in Part I of potentially curable spinal cord disorders (pp 374-379)

PSYCHOMETRIC TESTS (T-1082)

Clinical Clues These studies may prove of great value in objectively separating the degree of neuroticism and the degree of organicity in the various chronic brain syndromes They are of particular help in evaluating post-traumatic syndromes cerebral atrophy and brain tumors that may simulate functional diseases (p 355)

The Wechsler Bellevue Intelligence Test

Technical Notes This test measures global intelligence without being greatly influenced by the patient s past formal educational background

The Bender Gestalt Test

Technical Notes This is a maturational test in visual motor Gestalt function It is intended to explore loss of function and to evaluate cerebral injury and disease

The Rorschach Test

Technical Notes This is a projective test employing standardized ink blots with which one may detect nuances in personality functioning that cannot be delineated by simpler methods

The Thematic Apperception Test

Technical Notes This is a story telling projective technique using pictures with suggestive plots It may be very useful in psychosomatic diagnosis by pointing out the drives conflicts relationships and environmental demands which influence the patient s thoughts and actions

OTHER STUDIES

Electroencephalography (217, 221, 225, 229)

Technical Notes Accurate technique the inclusion of a period of sleep in the recording and correlation for age states of consciousness metabolic abnormalities and medication are essential It must be appreciated that frequently there are no known underlying structural changes to account for observed abnormalities No good correlations have been found with intelligence, voluntary movements or psychic function Since abnormalities cannot be malingered it is of great potential value both clinically and for medicolegal purposes Follow up studies are often helpful

Clinical Clues Although this technique is diagnostic only of certain epilepsies (T-1085) it may prove helpful in localizing or evaluating early multiple sclerosis small strokes *Meniere s syndrome migraine the thalamic syndrome*

brain tumors,(T–1108) and chronic subdural hematomata in their atypical manifestations It is also abnormal in Addison s disease, the Cushing syndrome and hypothyroidism (T–30, 87) A normal electroencephalogram does *not* rule out epilepsy or organic brain disease, but probably signifies a better prognosis in the former (217)

Objective evidence of insufficiency involving the internal carotid and basilar arterial systems can be obtained by electroencephalographic studies during the lowering of the blood pressure with repeated postural tilting (tilt-table) and carotid compression Electroencephalographic slowing and other changes consistent with transient focal cerebral ischemia develop over the Sylvian area in patients with carotid artery insufficiency and over the regions supplied by the posterior cerebral arteries with basilar artery insufficiency (T–1088)

Electromyography (228)

TECHNICAL NOTES Electrical action potentials are picked up by percutaneous or needle electrodes, and are transmitted to a high gain amplifier and thence to an oscilloscope where their wave form can be seen Needle electrodes are essential for the diagnosis of lower motor neuron injury or disease Still or motion pictures can be made to secure permanent records This apparatus may also be used to re educate the muscles in patients with poliomyelitis

CLINICAL CLUES Normal skeletal muscle at rest exhibits no electrical activity The demonstration of skeletal muscle denervation in lower motor neuron disease by an involuntary fibrillation pattern at rest is the chief practical value of this procedure This change may not occur for as long as 21 days after the onset of the disease or injury

The electromyogram is also most valuable in differentiating lower motor neuron disease from disuse muscular atrophy, peripheral nerve injuries, upper motor neuron disease and primary muscle disease In the latter, the potentials are normal except for their decreased amplitude and rapid fading away when sustained contraction is attempted

While the electromyographic pattern is not diagnostic of amyotrophic lateral sclerosis it may be of considerable aid in making the diagnosis early in the course of this disease and in differentiating it from the myopathies localized lesions affecting the spinal cord and disorders which involve only the upper motor neurons The following features can usually be demonstrated in amyotrophic lateral sclerosis (1) fibrillation and fasciculation potentials in the skeletal muscles throughout the body (2) a reduction in the number and an increase in the size of motor unit action potentials and (3) a normal excitability and conduction of the remaining peripheral motor nerves (p 372) (T–1119)

Electromyography and nerve stimulation may aid in the differentiation of myasthenia gravis from the myasthenia associated with certain malignant tumors (T–1022) It is of added value in ruling out malingering and hysteria

Retinal Artery Pressure Determination (see Section XIII, p 809)

Therapeutic Diagnostic Tests (see Section XIV, p 811)

Provocative Tests (see Section XVI, p 823)

SECTION IX

Studies of Cardiovascular-Pulmonary Function

Circulation Time (262)

TECHNICAL NOTES This test is usually a very safe and valuable aid in evaluating myocardial efficiency The arm to-tongue time may be obtained with calcium gluconate or Decholin the arm to lung time with ether The normal arm to-tongue circulation time ranges from 10 to 16 seconds while the normal arm to lung time varies from 3 5 to 8 seconds

There have been untoward effects on occasion with all the drugs employed for determining circulation times These include arrhythmias in digitalized patients receiving calcium salts arrhythmias shock and hypersensitivity states with Decholin and venous thrombosis or sudden death with ether (particularly in patients with right to left shunts and with bronchial asthma)

Many other agents have been used with diverse end points including sodium cyanide fluorescein histamine, lobeline saccharin magnesium sulfate paraldehyde and radioactive materials The injection should be performed in one to two seconds after a lapse of at least 15 seconds from the time the tourniquet is released

CLINICAL CLUES A decreased arm to tongue time occurs in the presence of a shunt or fistula and in hyperthyroidism (even in the presence of heart failure) An increased arm to-tongue time usually occurs in congestive failure but it may be normal if the heart is not greatly enlarged or after a period of rest This study is unfortunately of little value in diagnosing preponderant right ventricular failure Normal arm to-lung times are usually encountered in cor pulmonale

It may be of value in differentiating certain types of congenital heart disease For example, the time is shortened in the cyanotic group when much of the circulation passes from the right ventricle to the aorta unless polycythemia is present

This study might also aid in differentiating the cardiac dilatation due to heart failure from the enlarged cardiac silhouette of pericardial effusion Similarly it may help to distinguish the anasarca or hepatomegaly of congestive failure from that due to other causes Polycythemia vera will usually prolong the circulation time, while significant anemia frequently shortens it A considerable prolongation of this time also occurs in myxedema

Venous Pressure (245, 257)

TECHNICAL NOTES Normally ranges from 50 to 150 mm water in the antecubital veins and up to 200 mm water in the femoral veins It is best determined

in the antecubital area with the arm held at a 45-degree angle, using a reference point 10 cm from the back The hepatojugular reflux should be utilized if early heart failure is suspected (p 239) The patient should also be made to exercise the forearm if a unilateral axillary or subclavian vein block is being considered

The venous pressure may be studied more accurately during the hepatojugular reflux test if the pressure and force applied over the hepatic area are quantitated as with the use of the 'hepatojugularometer" proposed by Burch (T-833j) A pressure of 50 mm of mercury will usually raise the venous pressure in the presence of heart failure

CLINICAL CLUES Elevated in all the veins in right-sided failure, and in pericardial effusion or constriction Elevated in the arm veins but normal in the leg veins in aortic aneurysm, mediastinal masses and thrombosis of the superior vena cava Normal in the arm veins and increased in the leg veins in inferior vena caval invasion, thrombosis, or compression This determination may occasionally be helpful in differentiating early shock from heart failure in acute myocardial infarction when doubt exists

Electrocardiogram (258, 271)

TECHNICAL NOTES In addition to the numerous cardiac and non cardiac conditions in which it is of value, an electrocardiogram should be taken routinely in the diagnosis or followup of patients with myxedema diphtheria and electrolyte disturbances (237) Always remember that the EKG does *not* positively dictate diagnosis or prognosis, and that overemphasis of minor variations can lead to much needless anxiety (T-1157) Numerous nonpathologic factors can alter many components of the EKG, including exercise ingestion of food, smoking, changes in posture (T-882) and deep breathing (270)

With suspected recent angina, it is very important to utilize as many sites for the exploring electrode as appears necessary when the usual 12 leads are not conclusive Particular emphasis is placed on the high lateral and ensiform leads in this regard

The exercise tolerance test and the anoxemic test for coronary disease are considered in Section XVI (p 822)

CLINICAL CLUES Individuals with apparently normal hearts may have a right bundle branch block and delayed A V conduction Hypothyroidism and adrenal insufficiency should be suspected if unexplained low voltages are present Increased or decreased potassium concentrations are often suspected from abnormal ST segment and T wave configurations Diphtheritic myocarditis should be suspected if marked electrocardiographic changes occur after a recent sore throat with or without an associated polyneuritis Cardiac metastases or leukemic infiltrations might be suspected if arrhythmias, conduction disturbances, or pericarditis occur in these conditions Hyperthyroidism should be suspected in auricular fibrillation without apparent cause

Although it is true that most myocardial infarctions are obscured by the presence of a left bundle-branch block this should not be regarded as an inviolate truism For example in such a situation there may be highly suggestive Q waves in leads I, aV_L and V_6 along with an abnormal precordial R wave progression in an extensive anteroseptal infarction (243) Similarly a notched R wave or an R′ in aV_F and lead III are often associated with posterior infarction

Ballistocardiography (239, 244, 272, 273, 278)

TECHNICAL NOTES Various apparatus are now available to measure body motion in its displacement, velocity, and acceleration components Curves are vari

ously labeled from points designated as H_1 I J, K, and L They are observed for amplitude notching displacement, and deterioration after expiration, smoking, or exercise There is a wide range of normalcy

CLINICAL CLUES This procedure may prove helpful in the evaluation of coronary disease or unexplained attacks of rapid heart action occurring below the age of 50 It is still regarded as an experimental technique by most clinical cardiologists, however An early M pattern is the abnormality most consistently found in the presence of advanced coronary heart disease

Two other manners in which the ballistocardiogram can be of aid in evaluating patients with known coronary disease are the appraisal of the functional recovery of the myocardium after convalescence and the establishment of some evidence for a previous infarction when the old tracings are not available and the current tracings appear normal (272b)

Vectorcardiography (*256, 280a, b*)

TECHNICAL NOTES Specialized equipment is required with which the balance of electrical forces throughout the cardiac cycle are inscribed in the form of vector loops

CLINICAL CLUES This technique is still primarily of a research nature although it may ultimately be incorporated into clinical cardiology Its main value is the clarification of unusual strain and coronary patterns that are encountered in conventional electrocardiograms

Phonocardiography

TECHNICAL NOTES Various microphones are employed along with selective filters and other devices to enable one to correlate auscultatory perception with phonocardiographic registration For practical purposes the tracings in two bands (70 to 110 and 150 to 200) are ordinarily adequate Low pitched rumbles may be recorded poorly on the phonocardiogram however

CLINICAL CLUES In addition to helping in the definition of heart murmurs *phonocardiography can aid in the analysis of gallop rhythms splitting of the heart* sounds and other cardiac sounds in congenital and acquired heart disease Phonocardiography might provide a ready and objective criterion for both the severity of mitral stenosis and the actual improvement that occurs following a mitral valvuloplasty (T-857d) Provided the heart rate is not too slow the most reliable criterion is the index derived from the delay of the first heart sound (with reference to the onset of the QRS complex) and the interval between the second heart sound and the opening snap (Q 1 2-OS)

The Valsalva Maneuver (260, 274)

TECHNICAL NOTES The patient in the supine position blows into a mouth piece connected to the anaeroid attachment of a clinical blood pr ssure cuff with sufficient strength to maintain the pressure steadily at 40 mm of mercury for approximately 10 seconds The systolic blood pressure in the arm is determined at rest and during the four phases of the ensuing response The time and rate of fall from phase 1 to phase 2 and the presence or absence of an overshoot in phase 4 are determined The normal response is divided as follows

Phase 1 (the strain phase)—a sudden increase in the systemic arterial pressure for 1 to 2 seconds

Phase 2—systemic and pulse pressures fall

Phase 3 (completion of forced expiration)—a sudden fall in the systemic arterial pressure

Phase 4 (after the release of forced expiration)—a characteristic rise ('over shoot') in the arterial systolic, diastolic and pulse pressures within 3 to 8 seconds, followed by a bradycardia

The response can be properly interpreted only if the venous pressure is normal or but slightly elevated, and if no delay in the onset or cessation of the forced expiration occurs

CLINICAL CLUES This maneuver has been advocated as a clinical test for borderline pulmonary congestion in the absence of severe right ventricular failure In this condition (1) systemic pressure is maintained abnormally with no fall, usually throughout the entire strain period and (2) reflex bradycardia or over shoot does not occur with the release of forced expiration

It may also be of value in evaluating dyspnea, diuretic therapy, effectiveness of mitral commissurotomy, and in detecting incipient pulmonary congestion in elderly patients receiving fluids parenterally

Carotid Sinus Pressure Trial (361)

TECHNICAL NOTES Unilateral pressure is exerted over the carotid bifurca tion for 10 to 15 seconds with the patient sitting upright The patient should count aloud An electrocardiographic control should be used when a rhythm disorder is present

CLINICAL CLUES The clinical and electrocardiographic response can be diagnostic of auricular flutter and paroxysmal auricular tachycardia This maneuver may also stop an attack of angina pectoris (even when not due to an associated rapid heart action) by interrupting either the sympathetic reflex arcs or the sensory pathways

This is also a valuable technique in the differentiation of gallop rhythm from other types of triple rhythm Whereas the true gallop sound invariably becomes inaudible when the ventricular rate is slower than 91 per minute the other extra sounds usually become more obvious because of the changes in timing intensity, or clarity (265)

Screening Test for Unilateral Renal Disease in Hypertension (I)

TECHNICAL NOTES The urine from each ureter is simultaneously collected after previous hydration (200 ml water every 15 minutes for 1 hour preceding the test) The volumes and sodium concentrations are determined and compared Care must be taken to avoid bladder leakage and to insure an adequate urine flow The volume of urine and the concentration of sodium should be either the same or proportionately comparable from each kidney This applies when the kidneys are normal and when bilateral renal disease is present The test is contraindicated in the presence of azotemia The patient should have been on a regular salt diet for the previous 3 to 4 days

CLINICAL CLUES In this study of *total* renal damage a unilateral reduc tion in both the urine output and the sodium concentration not only suggests the diagnosis of unilateral renal hypertension but also may prognosticate the beneficial effects to be derived from a nephrectomy (73) (T–887b)

This test is also indicated in hypertensive patients without obvious renal disease who either exhibit severe or accelerated hypertension, or whose response to anti hypertensive medication is very poor It is considered positive if the urine volume is reduced by 60 per cent or more and if the sodium concentration is reduced by 16 per cent or more in the urine coming from one kidney as compared with that from the other

The radioactive Diodrast renogram in which external monitors measure the

rates of accumulation and disappearance of I^{131} labeled Diodrast over the renal areas after an intravenous injection of the test material, also holds much promise in the detection of unilateral renal disease (88)

Screening Test for Unilateral Renal Vascular Disease in Hypertension (II)

TECHNICAL NOTES Tetraethylammonium chloride (TEAC) is injected intravenously, following which the blood pressure is checked at 1 minute intervals

CLINICAL CLUES Whereas patients with essential or nonrenal hypertension, or irreversible renal vascular disease will exhibit a drop in blood pressure, either a rise or no fall might be observed in unilateral renal vascular and humoral hypertension Such a paradoxic response has also been interpreted as indicating potential reversibility of the hypertension by surgery (T-887a)

Measurement of Skin Temperatures

TECHNICAL NOTES Special skin thermometers or thermocouples are employed to record the skin temperatures before and after the release of sympathetic tone by a variety of methods (paravertebral blocks ganglionic blocking drugs, raising the body temperature) A cool room (18 to 20 C) is desirable

CLINICAL CLUES The objections to this test are overcome by its relative simplicity and overall accuracy A rapid rise to 31 to 33 degrees C indicates a normal blood supply The absence of a rise usually indicates occlusive vascular disease An intermediate response is probably indicative of both reflex sympathetic vasoconstriction and occlusive vascular disease

CARDIAC CATHETERIZATION STUDIES (247, 251)

RIGHT HEART CATHETERIZATION

TECHNICAL NOTES A number of the difficulties that might be encountered with right-heart catheterization—and which could therefore lead to erroneous conclusions—have been summarized by Fowler Mannix and Noble (251b) The failure might be technical as with the abutting of the catheter tip against the arterial wall or the occlusion of the catheter On the other hand, it might be one of interpretation For example an increase in the oxygen content of the blood in the pulmonary artery in comparison with that in the right ventricle could be variously due to a ventricular septal defect a patent ductus arteriosus anomalous pulmonary arteries or contamination of the sample by pulmonary venous blood

CLINICAL VALUE Evaluation of congenital heart disease particularly left to right shunts (patent ductus arteriosus, atrial septal defect and ventricular septal defect)

Evaluation of both the presence and degree of stenosis of the various valves (pulmonary mitral and tricuspid)

Diagnosis of anomalous vessels (anomalous pulmonary veins entering the right atrium persistent left superior vena cava dextroposition of the aorta and patent ductus arteriosus)

Diagnosis of insufficiency of the tricuspid and mitral valves right and left ventricular failure high-output failure pericardial constriction and cardiac tamponade cor pulmonale (cardiac catheterization is most risky in patients with essential pulmonary hypertension) (T-874)

Differentiation of arterial oxygen unsaturation due to emphysema and that due to a right to left shunt

Preoperative and postoperative evaluation of cardiac surgery

A hemodynamic differentiation between constrictive pericarditis and myocardial fibrosis may be possible (p 233) (T-851d)

Right Atrial Mean Pressure

NORMAL RANGE 0 5 mm of mercury

Right Ventricle

NORMAL RANGE Systolic pressure, 18 to 30 mm of mercury, diastolic pressure, 0 to 5 mm of mercury

Pulmonary Artery

NORMAL RANGE Systolic pressure, 18 to 30 mm of mercury, dia tolic pressure, 6 to 12 mm of mercury

Pulmonary "Capillary" Mean Pressure

NORMAL RANGE 6 to 12 mm of mercury

Pulmonary Arteriolar Resistance

NORMAL RANGE 47 to 160 dynes sec/cms^{-5}

Mitral Valve Cross Sectional Area

NORMAL RANGE 4 to 6 sq cm

Limit of Variation in Oxygen Content from One Chamber to Another

NORMAL RANGE Superior vena cava—right atrium, 1 9 vol %, right atrium—right ventricle, 0 9 vol % right ventricle—pulmonary artery, 0 5 vol %

Cardiac Index

NORMAL RANGE 3 1 ± 0 4 L/min /m^2

Cardiac Output

NORMAL RANGE 5 ± 0 5 L/min

LEFT-HEART CATHETERIZATION (259) (T-856c d)

TECHNICAL NOTES The concomitant performance of left-atrial catheterization and right-sided catheterization has yielded definitive preoperative data concerning the presence of mitral stenosis or regurgitation and aortic stenosis in an increasingly large group of patients There is relatively little risk if performed by a trained person Two needles are passed into the left atrium, through which fine catheters are introduced in order to obtain pressure recordings

CLINICAL VALUE A pressure gradient in diastole from the left atrium to the left ventricle is the hallmark of mitral stenosis A significant pressure gradient

between the left ventricle and the brachial artery or aorta during systole establishes the diagnosis of aortic stenosis

In many instances left-sided catheterization has pointed out the lack of correlation between the pulmonary capillary pressures obtained by right-sided studies and the pressures in the left atrium A postvalvuloplasty restenosis of the mitral valve can be diagnosed much earlier with this technique (T-857c) The success of various valvuloplasty procedures postoperatively can also be so ascertained

X RAY STUDIES

Fluoroscopy of the Heart and Lungs

TECHNICAL NOTES Ample time for accommodation of the eyes is vital for accurate fluoroscopy More than 4 m a are usually not necessary The chest is examined in all phases of inspiration and expiration and in the various rotational positions It is also examined after coughing and sniffing (for diaphragmatic motion) and after the ingestion of a thick barium preparation

CLINICAL CLUES This examination is essential for the accurate diagnosis of certain cases of acquired and congenital heart disease lung disease pulmonary function and disease of the diaphragm ribs pleura thoracic spine and other chest structures The importance of repeated studies and caution in their interpretation cannot be overemphasized It has been shown that there is a tendency for the displacement of the esophagus due to the enlarged left atrium in mitral stenosis to lose its characteristic localized form as the heart enlarges Furthermore there may be no relationship between the degree of esophageal displacement and the volume of the left atrium (277)

Chest Films (236, 240, 241, 268, 269) (T-425, 426)

TECHNICAL NOTES Good technique is very important (One should be able to just make out the intervertebral spaces in the P A view) Standard films should be supplemented by lateral oblique lordotic (255) lateral recumbent (279) stereoscopic and other views as indicated They may be further supplemented by bronchography spot films expiratory films and overexposed Bucky films They should be repeated frequently if an evolving process is suspected

Many studies have affirmed Fleischner s observation that the anteroposterior lordotic position may be of great value in the diagnosis of atelectasis of the right middle lobe (T-539c) Some difficulty might arise however in distinguishing this disorder from a mediastinointerlobar pleurisy with effusion when this same area is affected

The silhouette sign has proved to be most helpful in localizing intrathoracic lesions from the posteroanterior roentgenogram (250) (This is because an intrathoracic lesion anatomically contiguous with a border of the heart or aorta will obliterate that border) Thymus enlargement in young children often disappears when a good inspiratory film is obtained

The use of newer contrast media such as Visciodol (a Lipiodol sulfanilamide suspension) has increased the safety and speed of bronchography enabling one to obtain excellent bronchograms with very little penetration of the alveoli (264)

When the conventional upright inspiratory and expiratory films of the chest are not revealing the presence of a suspected small pneumothorax can often be demonstrated by placing the patient in the lateral decubitus position The costophrenic sinus sign of pneumothorax—consisting of the ballooning out of the potential space between the diaphragmatic and costal pleurae by the free pleural air—may be shown by this technique (233)

Clinical Clues These radiograms constitute a basic diagnostic necessity for diseases of the heart, lungs, pleura, ribs, diaphragm, mediastinum, and thoracic vertebrae They may also occasionally indicate lesions in the neck, shoulder girdle, spleen, stomach (through the gas bubble), and liver A hiatal hernia can at times be detected in the plain film (263)

The presence of a very small heart size should make one suspicious of Addison's disease (333) Violent exercise or a rest in bed for several weeks can significantly reduce the heart s transverse diameter Pericardial fluid usually cannot be detected until 500 ml or more is present

A widened azygos vein (i e greater than 10 mm) may be seen at the junction of the right main bronchus and trachea, and is a reliable sign of pulmonary vascular congestion (T-832) It has also been found in cirrhosis of the liver (p 98)

The diagnosis of anomalous pulmonary venous drainage may be suggested even prior to cardiac catheterization and angiocardiographic studies by the figure-of 8" *configuration of the heart and mediastinum in the P A projection, and the asso* ciated evidence of large anomalous draining veins from the right lower lobe crossing in front of the esophagus to the left side of the mediastinum (T-1058b)

Refer to Group IX of Part I for a discussion of buckling' of the great vessels (pp 300 and 301), and to Group XI for the differential diagnosis of nonmalignant conditions simulating lung tumors (p 334) The presence of calcification within a lung mass does *not* exclude a carcinoma (T-1059) The differential diagnosis of mediastinal tumors is also considered in Part I (pp 336 to 343)

Laminograms may be of great value in identifying calcification in the lungs or heart (240 276) small metastatic nodules, and cavities or other abnormalities affecting the trachea and major bronchi within dense areas of consolidation *It is* cautioned that there may be considerable difficulty in differentiating with certainty the open negative from the closed negative cavity in pulmonary tuberculosis by *laminography (T-546b) When there is heavy calcification of one heart valve,* there is usually organic involvement of a second one (277) A pulmonary arteriovenous fistula can occasionally be demonstrated with great clarity by laminography (240) Planigrams in the semioblique position have occasionally been helpful in visualizing mediastinal invasion from a lung cancer when vertical planigrams were inconclusive

In most instances, 'tenting of the diaphragm is the result of small areas of atelectasis at the base of the lung and has no relationship to adhesions *A funnel* chest should be considered when the following features are present in the P A chest film straightening of the left border of the cardiac shadow, an appearance *simulating consolidation in the middle lobe of the lung, and clear visualization of the lower thoracic section of the spinal column* (240)(T-877)

Refer to Group IV of Part I for an etiologic classification and analysis of atypical pneumonitis (pp 119 to 132) The finding of aerated bronchi within an area of consolidation is usually diagnostic of pneumonia Careful follow up studies are mandatory in cases involving a delayed resolution of pneumonia (T-423) The cylindrical dilatation of the bronchi which may be noted for months following primary atypical pneumonia *is frequently completely reversible and is not neces* sarily an indication of true bronchiectasis

The visualization of submucosal infiltration by bronchography has been demonstrated in instances where bronchoscopy could not reach the area of the bronchogenic carcinoma Scleroderma and dermatomyositis may result in nodular lesions along the bronchial distribution in the lower lung fields Pleural tumors producing effusions can be demonstrated by the induction of a diagnostic pneumothorax after the pleural fluid is aspirated

Phlebography

TECHNICAL NOTES One of the standard radio-opaque contrast media is rapidly injected intravenously (usually 30 ml) with radiographs being taken during and immediately following the infusion The only disadvantage in using the veins in the antecubital fossa is the possibility of an error in interpretation when an obstruction occurs solely in the axillary or brachial veins If a persistent left superior vena cava is suspected, the contrast medium should be injected into the left arm veins

CLINICAL CLUES This technique is particularly valuable in evaluating obstruction of the superior vena cava or the innominate veins and their major tributaries If the level of obstruction exists *above* the point where the azygos vein enters the latter may take over the function of the superior vena cava in returning blood from the upper part of the body When the obstruction occurs *below* the azygos vein the blood returns to the heart via the inferior vena cava, with extensive collaterals being formed on the thorax and abdomen

Angiocardiography (246)(T-916)

TECHNICAL NOTES Contrast media (Diodrast 70 per cent Hypaque-M 90 per cent) are injected intravenously Films are taken in rapid succession by various multiple exposure techniques over the area being studied Repeat studies should be performed only with a full appreciation of the large amount of radiation the patient receives It is possible that further developments with the use of intravascular injections of *pure* carbon dioxide may provide another means of contrast roentgen visualization of the intracardiac structures including the status of the pericardium (242)

CLINICAL CLUES These films may be diagnostic of anatomic and physiologic derangements in the heart lungs mediastinum and great vessels They are also particularly useful in evaluating congenital heart disease (especially the cyanotic types) the superior vena caval syndromes mediastinal tumors and aortic aneurysms Even aneurysms of the aortic sinuses can be clearly delineated (T-901 1256) Once diagnosed pulmonary arteriovenous fistulae may be excised and cured

Retrograde brachial aortography employing 35 per cent Diodrast has a high yield of certain operable lesions in infancy (patent ductus arteriosus, coarctation of the aorta) when careful attention is paid to the indications and diagnostic pitfalls of this procedure (234)

Abdominal Aortography (248, 266, 275)

TECHNICAL NOTES When indicated this is a potentially valuable procedure in experienced hands It is performed under pentothal anesthesia A 6 inch 18-gauge needle is used which is introduced below the left twelfth rib 6 to 8 cm lateral to the spinous process of the corresponding vertebra Films are taken with a rapid cassette changer The aorta is best visualized in the first second, while maximal filling of the vessels occurs at three to four seconds

Even with experience however there is a definite risk of either serious renal injury or paraplegia with the use of the presently available contrast media It is wise to take a film after 2 ml of the dye have been given in order to rule out filling of the superior mesenteric artery If one sees a nephrogram following aortography major vascular surgery should be delayed for 4 to 5 days to be sure that no serious renal damage was produced There is less apprehension now concerning the possibility of rupture when translumbar aortography is considered in the presence of either an aneurysm or extensive calcification of a normal sized aorta (248b)

In one survey of 13,207 abdominal aortograms, the most frequent complications consisted of (1) renal damage, usually the result of excessive injections, direct renal artery injections, or injections in patients with high aortic obstruction and (2) neurologic damage, usually caused by either excessive injections of the medium, or proximity of the needle tip to the major anterior radicular artery—most often at the level of L-2 (75b)

CLINICAL CLUES If a homograft is anticipated, this can serve as a valuable diagnostic technique for the precise visualization of the location and extent of either the segmental obstruction or aneurysm of the aorta and its major branches (T-911) Aortography may not be helpful in the delineation of an arteriosclerotic abdominal aortic aneurysm due to the presence of a relatively normal lumen within large mural thrombi

BLOOD GASES (RESTING)

Arterial

OXYGEN CONTENT

NORMAL VALUES 16 to 20 vol per cent
CLINICAL CLUES Increased in polycythemia vera Decreased in anemia, emphysema pulmonary edema asthma, and congenital heart disease The difficulty in accurately detecting or interpreting cyanosis clinically has been conclusively shown (T-883n)

OXYGEN HEMOGLOBIN CAPACITY

NORMAL VALUES 17 to 21 vol per cent
CLINICAL CLUES Increased in polycythemia vera Decreased in anemia carbon monoxide poisoning and methemoglobinemia

OXYGEN SATURATION

NORMAL VALUES 96 to 100 per cent
CLINICAL CLUES Decreased in respiratory obstruction, pulmonary edema, congenital heart disease and high altitudes In the presence of normal hemoglobin values the majority of observers are unable to detect cyanosis until the arterial oxygen saturation falls to 80 per cent

CARBON DIOXIDE CONTENT

NORMAL VALUES 45 to 51 vol per cent (whole blood)
CLINICAL CLUES Increased in respiratory obstruction emphysema, pulmonary edema, and congenital heart disease (elevated HCO_3) Decreased in hyperventilation If it remains elevated despite acute hyperventilation, the possibility of alveolar hypoventilation due to an impaired sensitivity of the respiratory center arises (p 234) (T-842a)

Venous

OXYGEN CONTENT AND SATURATION

NORMAL VALUES 10 to 16 vol per cent and 60 to 80 per cent respectively
CLINICAL CLUES Increased in hyperventilation, fever, and hyperthyroid

ism Decreased in respiratory obstruction pulmonary edema, cardiac failure anemia, carbon monoxide poisoning methemoglobinemia high altitude and exercise

CARBON DIOXIDE CONTENT

NORMAL VALUES 55 to 74 vol per cent

CLINICAL CLUES Increased in heart failure and the causes listed under arterial carbon dioxide content Decreased in hyperventilation

Arteriovenous Oxygen Difference

NORMAL VALUES 4 5 ± 0 7 cc per 100 ml

CLINICAL CLUES Increased in the presence of shunts, exercise, and various types of anoxia

Oxygen Consumption

NORMAL VALUES 110 to 150 ± 30 cc min /m²

CLINICAL CLUES Increased in compensatory hyperventilation and hyper metabolism

Alveolar Arterial Difference (pO_2)

NORMAL VALUES 9 7 mm of mercury

CLINICAL CLUES May be increased in disorders of pulmonary ventilation and diffusion Alveolar capillary block is evidenced by a marked increase after exercise Also increased by the shunting and venous arterial admixture in poly cythemia

Arterial Oxygen Saturation Studies in Clinical Hypoxemia (252, 261)

NORMAL VALUES The values of arterial oxygen saturation are recorded by oximetry at intervals while resting during exercise and when breathing 90 to 95 per cent oxygen

CLINICAL CLUES This is still a research procedure but the inferences derived from these studies bear considerable clinical import in cor pulmonale emphysema primary and secondary polycythemia pulmonary hypertension alveolar-capillary block and venous arterial shunts by passing the pulmonary circulation

PULMONARY FUNCTION STUDIES (254)

Ventilation Rate, Basal

NORMAL RANGE 2 5 to 5 0 l /min /m²

TECHNICAL NOTES May be obtained in various ways, but most conveni ently by the use of an 11 liter (or larger) Benedict-Roth spirometer

CLINICAL CLUES Decreases with age Increased by compensatory hyper ventilation due to many causes

Fluoroscopy of the Chest (249, 236)

TECHNICAL NOTES See comments above under X Ray' in this section

CLINICAL CLUES This study is very important in screening and evaluating

the behavior of the ribs, diaphragm, pleura, parenchyma, and airways It is particularly helpful in detecting "trapping" and mediastinal shifts (p 455)

Vital Capacity—Timed (V C Is "Expiratory Reserve Volume" Plus "Inspiratory Capacity") (253)

NORMAL RANGE 95 per cent or more of the predicted vital capacity within 3 seconds Males 3 to 5 liters Females 2 5 to 4 liters

TECHNICAL NOTES The Gaensler modification of the spirometer using an electronic timer is best employed A bronchodilator aerosol may be administered prior to the test in order to evaluate the degree of "bronchospasm"

CLINICAL CLUES This procedure tests the elastic properties of the lung The total timed vital capacity and a study of the spirogram tracing (if recorded) are valuable in the diagnosis of early clinical emphysema This is enhanced if a *maximum* breathing capacity is concomitantly performed It is also helpful in evaluating the effects of therapy in asthma, emphysema, and heart failure

Walking Ventilation (W V)

NORMAL RANGE 12 to 19 L/min

TECHNICAL NOTES A high velocity, one way valve and a 100 liter Douglas bag are used The volume is measured over 3 minutes with the patient walking at a rate of 180 ft per minute

CLINICAL CLUE This index remains remarkably constant The value of the test is enhanced by its simplicity if the apparatus is available

Maximum Breathing Capacity (M B C)

NORMAL RANGE Males 100 to 160 L/min Females 70 to 130 L/min

TECHNICAL NOTES Performed over a 15 to 30 second period A bronchodilator aerosol may be administered prior to the test in order to evaluate the degree of "bronchospasm" (In a sense, this index is not physiologic owing to its limitation by the cardiac output)

CLINICAL CLUES This procedure tests the lung "resistance" It is a very valuable index of total lung function *if* the patient can cooperate fully It is particularly helpful in evaluating the operative risk during and after lung surgery It may not be greatly reduced in "alveolar capillary block" however

Walking Index

NORMAL RANGE 10 to 20 per cent

TECHNICAL NOTES Computed as $\frac{\text{W V}}{\text{M B C}} \times 100$

CLINICAL CLUES Dyspnea begins at approximately 35 per cent, and is severe when the maximum breathing capacity is reduced to twice the walking ventilation

Residual Air Volume

NORMAL RANGE 20 to 35 per cent of the total capacity

TECHNICAL NOTES Various methods of determining this volume are employed, using either the open or closed circuit techniques

CLINICAL CLUES Emphysema is present when this index is greater than 35 per cent

Alveolar Nitrogen after Breathing 100% Oxygen for 7 Minutes (238)

NORMAL RANGE Less than 2.5 per cent nitrogen (usually less than 1.5 per cent)

TECHNICAL NOTES This test is a relatively simple index of intrapulmonary mixing" A closed circuit and nitrogen meter are employed

CLINICAL CLUES A reading greater than 2.5 per cent nitrogen indicates emphysema

Differential Bronchospirometry

NORMAL RANGE

RIGHT LUNG	PER CENT OF TOTAL
Oxygen uptake	52–58
Ventilation	52–58
Vital capacity	52–58
Total lung capacity	52–58

TECHNICAL NOTES Various catheters are introduced into the trachea under fluoroscopic control, at least 2 cm and not more than 4 cm into the left main stem bronchus Contraindications include recent hemoptysis tracheobronchial deformities strictures of the left main stem bronchus an ulcerative tracheobronchitis and the presence of marked cough secretions or dyspnea

CLINICAL CLUES This study is occasionally very important in evaluating the operative risk in thoracic surgery when bilateral disease of the lungs is present Under these circumstances marked discrepancies can occur between ventilation oxygen uptake and the x ray appearance

Air Velocity Index

NORMAL RANGE 0.8 to 1.2

TECHNICAL NOTES This index is not actually a test of pulmonary function *per se* It is determined by the ratio per cent M B C /per cent V C

CLINICAL CLUES The ratio is less in obstructive insufficiency (asthma emphysema) The ratio is higher in restrictive insufficiency (pleural effusion pneumonectomy and pneumothorax)

SECTION X

Exfoliative Cytology [287, 290, 294, 299]

Exudate or Transudate Fluid Aspiration From the Pleural Space, Pericardium, Peritoneal Cavity, Spinal Fluid, Retrouterine Space, and Breast Cysts

TECHNICAL NOTES A specimen (preferably 20 to 50 ml) is obtained and preserved immediately upon collecting by adding an equal volume of 50 to 95 per cent ethyl alcohol or 10 per cent formalin The specimen must be centrifuged at once and refrigerated if there is any delay in processing Mesothelial cells and histiocytes present the chief stumbling blocks in the interpretation of smears or sections of cell blocks both of which procedures should be performed (288)

CLINICAL CLUES The histologic findings derived from examinations of these fluids are valuable in indicating the presence of metastases from primary malignancies in the lungs pleura, gastrointestinal tract, and genitourinary organs There is an overall diagnostic accuracy of about 50 per cent when malignant tumor is actually the cause of serous effusions These studies are also helpful in excluding malignancy in ovarian fibroma (the Meigs Cass syndrome), hepatic and cardiac failure thrombosis of the inferior vena cava and Chiari s syndrome (when not due to cancer) In the absence of diagnostic cells, the concomitant finding of pleural fluid glucose levels of 26 mg per cent or lower is highly suggestive of a tuberculous effusion (300) Extraction with ether can differentiate chylothorax from the haziness commonly observed with pleural transudates

Transudates characteristically have a specific gravity of less than 1 018, a total protein content that does not exceed 2 5 gm per 100 ml and a glucose content of from 80 to 100 mg per 100 ml On the other hand, exudates usually have a specific gravity of more than 1 018 a total protein of the supernatant fluid after centrifugation in excess of 3 0 gm per 100 ml, and lower glucose levels (due to the glycolytic activity of the cells and bacteria)

Nipple Smears

TECHNICAL NOTES A few drops from the nipple are gently expressed or aspirated onto a clean glass slide They should be smeared directly and allowed to dry, but promptly placed in 70 per cent alcohol

CLINICAL CLUES Statistics on the reliability of this technique are scant The yield is low in cancer detection Intraductile papillomas and duct-cell carcinomas are the tumors most readily diagnosed this way

Prostatic Secretions (289)

TECHNICAL NOTES Thin even smears are made on albumen glycerol slides after prostatic massage They are immersed in an ether alcohol fixative One may also study the first-voided urinary specimen

CLINICAL CLUES This technique may prove to be helpful in evaluating nodules in the prostate and for in situ malignancies, but requires much more evaluation If ample secretions are obtained, an 85 per cent accuracy is said to be attainable

Skin (the Tzanck Test) (282, 299)

TECHNICAL NOTES Smears are prepared either from the vesicle fluid or from cellular material obtained by scraping the base of an early blister and allowing the specimen to dry in air The use of freshly diluted Giemsa stain following methyl alcohol fixation is probably the most satisfactory method of staining

CLINICAL CLUES Very large giant cells (balloon cells) in various stages of development are present in all early, newly formed vesicles in herpes simplex herpes zoster and varicella When positive one can confidently rule out smallpox, erythema multiforme pemphigus drug eruptions and other morphologically similar diseases Pemphigus vulgaris (toxic rounded epidermal cells with amorphous pyknotic nuclei) dermatitis herpetiformis (clumps of normal epidermal cells with a heavy eosinophilia) epidermolysis bullosa (few or no cellular elements) and other entities may also have fairly suggestive or diagnostic features

Skin (Touch Preparation Technique) (T-767d)

TECHNICAL NOTES The skin lesion is first cleansed with pHisoHex, rinsed with sterile saline and then wiped relatively dry with a Zephiran moistened sponge The superficial layers of skin are then scraped with a scalpel until an exuding surface results The secretions are collected onto a glass slide and finally stained with Wright s stain after drying

CLINICAL CLUES The large mononuclear cells characteristic of nonlipid histiocytosis (Letterer-Siwe disease) may be found in this manner The technique may also prove to be of value in diagnosing cutaneous leukemias lymphomas and other entities that are characterized by specific cell types

Sputum and Bronchial Aspirations (295)

TECHNICAL NOTES Sputum should be obtained freshly and after deep coughs into a wide-mouthed bottle It should be collected in 70 per cent ethyl alcohol over 24 hours Opaque pieces of tissue or blood flecks are the most rewarding for study Atropine should be avoided before bronchoscopy and bronchial aspiration The secretions so obtained are fixed in an equal volume of 95 per cent alcohol

CLINICAL CLUES The reliability is very high if three 24 hour specimens are studied particularly in the epidermoid and anaplastic cancers of the lung Fat may be noted in the sputum on the third day after fat embolism (T-792 794) Mineral oil can be detected both histologically and by the gross grease spots when lens or cigarette paper is applied (292) The presence of considerable and long standing pulmonary infection can result in false positive cytologic reports of the bronchial secretions (T-463a)

Synovial Fluid (296)

TECHNICAL NOTES The knee is the joint most frequently aspirated, either medial or lateral to the patella The fluid is collected without anticoagulant, except for the specimen to be sent for cytologic analysis The determinations of most value include the gross appearance, cell count and structure bacteriologic examination, mucin and viscosity, and the sugar content Normally, synovial fluid is very viscous and clear, does not clot, contains only a few cells (mostly mononuclear), demonstrates a tight, ropy clump of mucin in a clear solution upon the addition of acetic acid and has a sugar content approximately that of blood

CLINICAL CLUES This type of examination can prove to be of great value in both the diagnosis and prognosis of obscure joint effusions, inasmuch as the synovial fluid reflects inflammatory changes in the adjacent synovial tissues It is of particular value in differentiating the majority of instances of severe inflammation due to rheumatoid and infectious arthritis from the arthropathies of trauma or degenerative joint disease With synovial inflammation, the fluid becomes less viscous is turbid, tends to clot, contains more cells, and has a lowered concentration of sugar

This technique is also highly valuable in distinguishing the septic arthritis complicating steroid therapy from a preexisting arthritic process (especially lupus erythematosus) for which the patient has been receiving these hormones (T-21d)

Urine

TECHNICAL NOTES Females must be catheterized Adequate centrifugation is needed Add 10 per cent formalin or 95 per cent ethyl alcohol in a volume equal to the specimen immediately after it is obtained Spread onto albumen glycerol slides It is wise to cover the smears with thin celloidin as soon as they are made in order to prevent detachment of the cells

CLINICAL CLUES Cytologic study on the urine is most important in the diagnosis of transitional cell carcinomas The interpretation is complicated by the frequent lack of differentiation in the transitional epithelium and the benign multinucleated cells that are commonly encountered (283)

Uterine-Vaginal Secretions

TECHNICAL NOTES Secretions are obtained either by vaginal aspiration or by using a cotton tipped applicator in the vagina or endocervix Smears obtained from the endocervix are more satisfactory than those from the posterior fornix (This apparently is due to the presence of the endocervical mucus plug in the former which collects a greater number of cancer cells)(300a)

Lubricating jelly must be avoided prior to the collection of the material The slides are immersed into a fixing solution of one half ether and one-half 95 per cent ethyl alcohol *before* they are dried They are kept in the fixative 20 to 30 minutes (Because of the loss of much cellular material by this method, some pathologists are currently processing and examining smears that have been allowed to dry in air on specially prepared slides) The cervical surface biopsy spatula the diagnostic tampon, and the gelfoam sponge methods are also employed

The greatest value of the vaginal smear is in the evaluation of hormonal activity (Also see ' Studies of Endocrine Function in Section V, p 727)

CLINICAL CLUES A most valuable procedure for the early diagnosis of neoplasms affecting both the cervix and the uterine corpus Its reliability is very high in trained hands, with a low incidence of both false positives and false-nega

tives Competent cytologists have also been able to suspect the presence of an early ovarian carcinoma by positive vaginal smears (300b)

A high percentage of false positive cervical smears has been encountered when the cervical secretions are studied in women up to 2 months after childbirth These are the result of local infection childbirth trauma, and hormonal influences especially when the woman is breast feeding

As is the case with any smear of exfoliated cells that is interpreted as being positive pathologic confirmation by means of a formal biopsy should be obtained before radical surgery is performed Vaginal smears can also be utilized as an index of estrogenic activity by studying the nuclear pyknosis of the cells and the degree of keratinization It is pointed out however that estrogenic effects might be simulated by the presence of a chronic infection

GASTROINTESTINAL SECRETIONS (297)

Stomach (281, 284, 293)

Technical Notes The tube must be inserted to obtain the secretions from the distal third of the stomach The gastric juice is mixed with 95 per cent alcohol at once and centrifuged The gastric digestion can be checked to a large degree by the collection of the secretions into iced receptacles followed by immediate centrifugation and preparation of the smear It is important that no oily lubricants be used at the time of the intubation Gastric washings with physiologic saline offer a better chance of finding cancer cells from adenocarcinoma than do aspirations

Various clinicians also employ abrasive agents (balloons tubes, or bulbs), mucolytic agents (papain chymotrypsin) and the rotating gastric brush (under fluoroscopic control) Chymotrypsin lavage is achieved by introducing into the emptied stomach about 1 pint of the chymotrypsin solution for 10 minutes The solution is then aspirated and submitted for histologic study The use of atropine or histamine is of little added value

Clinical Clues There are a high number of *false-negative results (15 to 40 per cent)* even in the best of hands Satisfactory preparations are impossible in the presence of obstruction and gastric retention These techniques may become useful adjuncts in following patients with pernicious anemia and others who have had previous polyps of the gastrointestinal tract (297) This is particularly germane when considered in the light of the potential hazards of repeated semiannual x ray studies of the gastrointestinal tract

Gastric cytology is also helpful in strengthening the clinical impression of a benign ulcer resulting in the proper continuation of conservative management (284) Cytologic study may be of considerable help in the diagnosis of carcinoma involving the proximal third of the stomach (286)

Duodenum Biliary Tract (291)

Technical Notes Aspiration of contents in the descending duodenum is followed by fixation and centrifuging The careful cytologic examination of the duodenal contents may yield a higher degree of positive diagnoses when a pancreatic carcinoma is present if a preceding injection of secretin is given (T-154b)

Clinical Clues This technique may be helpful in diagnosing malignancy of the pancreas and biliary tree The indications for such duodenal drainage primarily include unexplained upper abdominal distress icterus or profound weight loss and back pain

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SECTION XI

Biopsies in Clinical Medicine

Bone (309, 319) (T-763, 764)

Technical Notes Material may be obtained from direct biopsy scrapings or by punch biopsy (particularly in the case of the spine) Either a Silverman or a trephine needle is utilized under fluoroscopic control depending on the location of the diseased site The plug of tissue is promptly placed in Zenker s fluid with glacial acetic acid

Clinical Clues May be diagnostic of neoplasms inflammations infections metabolic disorders the histiocytic reticuloendothelioses (eosinophilic granuloma, Hand-Schuller Christian disease), and the lipoidoses Bone biopsies in hyperparathyroidism usually show increased osteoblastic and osteoclastic activity along with fibrous proliferation

Bone Marrow (306) (T-689, 690)

Technical Notes Aspiration from various sites (the sternum spine iliac crest and tibia) can be very readily performed It should be repeated several times when isolated lesions are suspected This test is contraindicated in most of the hemorrhagic disorders A formal biopsy specimen should be obtained if the findings are inconclusive (See Hematologic Studies in Section I p 674)

Clinical Clues Very valuable in the diagnosis of the blood dyscrasias, metastases Gaucher s disease and certain infections (tuberculosis, brucellosis histoplasmosis) Thick gelatinous marrow occurs in primary amyloidosis A dry tap may be highly significant (fibrosis metastatic neoplasm lymphoma or infections) Typical cystine crystals are diagnostic of cystinosis

Breasts

Technical Notes One must biopsy a breast tumor not if it is typical of cancer but if it is not typical of a benign lesion This is especially true in the multinodular breast (mammary dysplasia) when either fixation of the tissues nipple changes or localized edema take place Bleeding from the nipple may also necessitate a biopsy Should large nodes (i e greater than 2 cm in diameter) be present in the axillary or supraclavicular areas along with suspected disease of the breast it may be wisest to biopsy the former first (314) There are a number of drawbacks to the triple biopsy procedure in which the primary lesion the axillary or supraclavicular nodes and the internal mammary lymph nodes are simultaneously biopsied

Colon (285)

TECHNICAL NOTES Smears can be made from either rectal scrapings or from saline washings which are obtained after adequate cleansing enemas Such cleansing enemas should have been completed 2 to 4 hours prior to the sigmoidoscopic examination The abdominal wall overlying the large intestine is massaged with deep pressure as the patient is rotated in the lateral decubitus positions About 250 ml of unheated 0 9 per cent saline are used This solution is then centrifuged and the sediment smeared onto several glass slides Smears are promptly fixed in ether alcohol The washings are preserved by adding an equal volume of 95 per cent alcohol

CLINICAL CLUES A study of these secretions may be of occasional value in following patients with previously removed polyps of the large bowel and in evaluating defects seen by x ray The feasibility of demonstrating malignant cells from carcinomas of all portions of the proximal bowel has been demonstrated (285)

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CLINICAL CLUES Necessary in the evaluation of unexplained solitary nodules in the breast, traumatic fat necrosis, and true gynecomastia or pseudo gynecomastia (i e , caused by fat deposition)

Duodenal and Jejunal Biopsies (T-153a)

TECHNICAL NOTES After gargling with pontocaine solution, the fasting patient swallows the small intestinal biopsy tube Within 1 to 2 hours, it can be directed into either the duodenum or jejunum under fluoroscopic control A con trolled negative pressure is induced by suction on a syringe, and biopsy is carried out according to the technique of Shiner The specimens in the knife blade or in the flexible part of the tube are immediately placed in formalin

CLINICAL CLUES This technique offers a method for both diagnosing and following disorders of the small intestine particularly idiopathic sprue and tropical sprue The histologic changes in these conditions are nonspecific, consisting chiefly of villous atrophy It may also be possible to diagnose secondary steatorrhea by this means

Endometrium (314)

TECHNICAL NOTES Endometrial curettage, producing specimens that are satisfactory for pathologic study can be performed readily by qualified physicians without hospitalizing the patient (Also see p 727 in Section V)

CLINICAL CLUES A proper endometrial biopsy may be of greater value in detecting an early uterine cancer than is the more indirect procedure of vaginal cytologic study It is of further aid in establishing the relationship between ovarian estrogenic and progestational activity when menstrual disturbances are present It should be noted however, that biologically detectable estrogens can still be present in the urine of patients with an atrophic endometrium

Fat (317) (T-970, 971)

TECHNICAL NOTES The nodules in the Weber Christian disease most often occur on the legs thighs abdomen and breasts

CLINICAL CLUES May be helpful in the diagnosis of relapsing febrile nodular nonsuppurative panniculitis and traumatic fat necrosis However, no true anatomic or histopathologic differentiation among the multiple types of Lipo-granulomas is usually possible

Gingiva (320) (T-202)

TECHNICAL NOTES Biopsy of the gingiva can be readily performed

CLINICAL CLUES May aid in the diagnosis of primary amyloidosis par ticularly if the intravenous Congo red test is not desirable (usually because of the presence of multiple skin lesions) When primary amyloidosis is suspected in the presence of inconclusive retention of Congo red the gingival biop y is also preferred to the liver biopsy in view of the possibility of severe hemorrhage following liver puncture (T-198)

Kidney (313, 316) (T-185, 187, 390)

TECHNICAL NOTES A modified Turkel or Vim-Silverman needle is em ployed with the patient in the prone position The specimen is considered adequate

if at least 10 glomeruli are present Although several large series have been reported with only a few complications, it is still generally considered experimental

Renal biopsy is usually contraindicated in the presence of the following renal tumor, hydronephrosis or pyonephrosis acute or suppurative perinephritis, uremia a solitary kidney a hemorrhagic diathesis and increased venous pressure secondary to congestive heart failure (313b) In patients with vascular disease, there is an added risk of perirenal hematoma following percutaneous punch biopsy of the kidney

CLINICAL CLUES This study may be of value in the diagnosis of intercapillary glomerulosclerosis chronic glomerulonephritis, nephrosclerosis, and such uncommon diseases of the kidney as amyloidosis metastatic carcinoma, polycystic disease and a toxic (chemical) nephrosis (T-238c) A membranous glomerulonephritis is found in about one third of the adults presenting with a nephrotic syndrome in whom there is no previous history of renal disease

In long term follow up studies by Smithwick and his associates a constant clinical correlation could *not* be demonstrated between the diffuse fibrinoid arteriolar necrosis found in renal biopsies in patients with essential hypertension and papilledema, the other clinical criteria of malignant hypertension or a uniformly poor prognosis (327)

Liver (T-323, 629)

TECHNICAL NOTES The intercostal approach is preferred by the author Biopsied tissue should be processed with additional stains for fat, iron and connective tissue The tissue should also be cultured when indicated The possibility of severe hemorrhage should be entertained when a punch liver biopsy is performed in the patient suspected of having a hepatoma

CLINICAL CLUES May be diagnostic of primary liver disease, lymphoma, metastases hemochromatosis the granulomata hematogenous tuberculosis schistosomiasis sarcoidosis histoplasmosis and brucellosis In patients with primary miliary tuberculosis of the liver who have been begun on specific therapy recognizable tubercles may be demonstrated in liver biopsy sections taken several weeks later (T-532a)

One should not mistake the pigment in the liver cells and the associated absence of inflammatory reaction which are found in the syndrome of chronic idiopathic jaundice with unidentified pigment in liver cells for bile stasis and obstructive jaundice (T-334)

Lung (I) (304, 324) (T-426, 443 447, 756, 765)

TECHNICAL NOTES At least 15 gm of lung tissue are required for pathologic bacteriologic and chemical analyses The biopsy procedure can be readily *performed by a chest surgeon (The anterior approach is* preferred if the disease is homogeneously diffuse The incision is usually limited to 3 to 5 cm in the third or fourth anterior interspace) Excisional biopsy of solitary circumscribed pulmonary nodules (coin lesions) and isolated circumscribed mediastinal masses may not only be diagnostic but curative as well

The Gomori methenamine silver stain has proved to be even more helpful than the periodic acid-Schiff stain *in establishing the diagnosis of histoplasmosis in* resected coin lesions of the lung It stains many degenerating forms of the organisms which would not be picked up by the latter method

CLINICAL CLUES Submission of the biopsied lung to definitive spectro-

graphic analysis may be important if an industrial poisoning is suspected (pneumoconiosis, beryllosis) Such tissue is also helpful in diagnosing tuberculosis, metastatic malignancy, sarcoidosis, and unexplained diffuse pulmonary lesions with fibrosis Tissues containing mineral oil have a characteristic histology and fluorescence after exposure to ultraviolet light in a dark room

Lung (II)

Technical Notes A needle biopsy of the lung is performed with the Vim Silverman needle The periphery of the tumor mass is biopsied under fluoroscopic control The specimen is crushed on a slide and fixed in ether alcohol

Clinical Clues This procedure should be reserved for patients with probable malignant tumors in the periphery of the lung, either primary or metastatic, in whom clinical evidence of incurability exists It is done only when a positive diagnosis has not been achieved either by exfoliative cytology or by bronchoscopic maneuvers This technique carries a definite risk of seeding the *malignancy through the needle tract*

Lung (III) (Carina)

Technical Notes A biopsy of the bronchial submucosa can be taken about ½ cm from the carina

*Clinical Clues This technique may determine the occurrence of lym*phatic spread in a lung malignancy and accordingly obviate a futile exploratory thoracotomy

Muscle (*322*) (*T–748, 944*)

Technical Notes One should search for macroscopic 'nodose' lesions to biopsy if polyarteritis is suspected Open biopsy is preferred (with the excision of a specimen measuring 2 x 1 x 1 cm) since segments of artery are needed to diagnose polyarteritis nodosa and other lesions In order to avoid fixation artifacts it is desirable to delay placing the tissue into fixative for one-half hour until the contractility and coagulability have lessened Bouin s solution is preferred

Clinical Clues May be diagnostic of polyarteritis, trichinosis dermatomyositis, and sarcoidosis Of little value in rheumatoid arthritis due to the nonspecificity of the "nodules in this tissue Muscle necrosis which is not associated with exudative phenomena is characteristic of idiopathic paroxysmal myoglobinuria The histologic changes in dermatomyositis may be quite variable, and can be mistaken for the myositis of the dyscollagenoses and certain types of late muscular dystrophy The demonstration of glycogen in the skeletal muscle of infants with enlarged hearts can aid in establishing the diagnosis of glycogenosis of the heart antemortem (T–829c)

Nickerson Kveim Test (T–749)

Technical Notes 0 1 to 0 2 ml of a heat-sterilized suspension of human sarcoid tissue (usually from the lymph nodes or spleen) is injected intradermally into the volar aspect of the forearm The test area is biopsied 4 to 6 weeks after the injection

Clinical Clues This technique is not completely reliable for sarcoidosis inasmuch as it has been frequently negative in this disease and positive in tuberculosis

Ovary

TECHNICAL NOTES Ovarian tissue and its stroma can be studied from the specimen removed by a wedge resection of this organ

CLINICAL CLUES Ovarian biopsy may be of aid in the evaluation of problems relating to infertility hirsutism and amenorrhea Such a procedure, if extended to the ovarian hilus might also be of considerable therapeutic value in patients with cortical fibrosis of the Stein Leventhal type (T-123 124)

Pericardium (318, 325) (T-849)

TECHNICAL NOTES A diagnostic and therapeutic pleuropericardial window is made as large and low as possible

CLINICAL CLUES This technique has not only proved to be diagnostic in cases of pericardial tamponade (particularly when due to tumors and tuberculosis) but has also served to decompress the area

Peripheral Lymph Nodes (302) (T-647, 648)

TECHNICAL NOTES Even small nodes can be diagnostic but one must be sure to identify and indicate their exact site for the surgeon When a lymph node biopsy is to be performed, the clinician should insist that the surgeon attempt to remove the fixed deep nodes with their capsules if possible rather than the more superficial nodes One should also try to avoid using inguinal nodes since changes resulting from previous infections may be confusing The left supraclavicular fossa should be examined routinely for a Virchow s sentinel node

CLINICAL CLUES Very valuable in the diagnosis of the leukemias, the lymphomas metastases, various bacterial infections sarcoidosis and the mycotic infections One may see a fibrinoid (but not a caseous) necrosis in sarcoidosis Lipomelanotic reticular hyperplasia is usually benign (T-670) Characteristic Schiff positive macrophages in the lymph nodes of Whipple s disease are said to be diagnostic (T-160) Two or more processes can affect the same node simultaneously (T-537)

Pleura (I) (304, 321)

TECHNICAL NOTES An oblong section of parietal pleura measuring approximately 1 5 by 3 cm is excised through an 8 cm intercostal incision The latter incision is made under local anesthesia in the anterolateral seventh or eighth interspace on the involved side

CLINICAL CLUES Open biopsy will usually be diagnostic for pleural effusions in which the cause (particularly tuberculosis) cannot be established by x ray or bacteriological methods Pleural biopsy may also be of aid in the diagnosis of malignancy and mycotic diseases of the chest

Pleura (II) (312)

TECHNICAL NOTES Needle biopsy of the pleura has been performed without significant complication in several small series of undiagnosed pleural effusions Biopsy of the parietal pleura may be taken at the time of the first thoracentesis After the pleural fluid is freely obtained the needle is withdrawn to the point at which the flow ceases and the distance is measured A Vim-Silverman biopsy needle is then introduced to this depth (indicated by the previous placement of a Kelly clamp at the desired level) The biopsy shaft is introduced until resistance

is encountered and then advanced 0 5 to 1 0 cm further Diagnostic material may even be obtained in the presence of a thickened pleura when no fluid can be aspirated The major contraindication to this procedure is a bleeding diathesis

CLINICAL CLUES This technique may prove to be a safe and convenient method of establishing the diagnosis of a pleural effusion—short of a thoracotomy—in both infectious and neoplastic disorders A granulomatous pleuritis can often be demonstrated in tuberculosis, sarcoidosis, histoplasmosis brucellosis, and tularemia Since a histologic diagnosis of nonspecific pleuritis does not exclude the possibility of an underlying tuberculous or neoplastic process, it is frequently wi e to perform an open biopsy (see above) when this diagnosis is made (312b)

Pre Scalene and Deep Cervical Lymph Nodes (304, 307, 311)

TECHNICAL NOTES Lymph nodes can almost always be obtained from the fat overlying the scalene muscle and along the subclavian and internal jugular veins into the upper mediastinum The deeper structures in the mediastinum can be visualized through the same incision by the insertion of a sigmoidoscope The potential complications of cervical mediastinal lymph node biopsy include the following pneumothorax from puncture of the apical pleura, phrenic nerve injury resulting in paralysis of the hemidiaphragm, air embolism via an open venous channel, local hemorrhage, lymphatic fistula, and injury to the brachial plexus

Bilateral excision of the fat pads increases the yield of diagnostic material, since cross lymphatic drainage commonly takes place When a choice exists in the face of bilateral disease, however, a biopsy of the fat pad on the right side of the neck is preferable (in view of the presence of the thoracic duct on the left and the dra n age of the lymphatics from the left lower lung to the right side of the neck)

CLINICAL CLUES These nodes may be the only accessible biopsy material—short of a thoracotomy—for many chest lesions particularly sarcoidosis lymphoma and bronchogenic carcinoma A positive biopsy helps to avoid a thoracotomy or pulmonary re ection when the lung cancer has already metastasized

Prostate (314)

TECHNICAL NOTES Attempts at punch needle biopsy of the prostate gland may not only miss a neoplastic focus but also engender the disadvantages of such a blind procedure when performed for suspected carcinomatous disease Only an open perineal biopsy should be recommended for patients with suspected malignant nodules

CLINICAL CLUES Cancer of the prostate develops most frequently in the posterior aspect of this organ Its peripheral location could preclude its identification by tissue removed at the time of an enucleation suprapubically or of a transurethral resection Prostatic secretions might also be studied (See p 789 in Section X)

Rectal Mucosa (323) (T–628)

TECHNICAL NOTES For the diagnosis of megacolon a segment measuring 5 to 10 mm is excised extending from the internal sphincter into the rectum Both the circular and longitudinal muscles must be included to study the ganglion cells

For diagnosis of parasitism a small piece of tissue containing mucosa and submucosa is removed from the first or second rectal valves with either a bladder punch or a rigid angulated cutting forceps After being compressed between two

glass slides, the specimen is examined for *Schistosoma* ova with the low power magnification of the microscope

Clinical Clues The biopsied tissue may be diagnostic in megacolon and in schistosomiasis This technique is particularly useful in Hirschsprung s disease where a very low lesion is present or after deactivation of the colon by a colostomy (which prevents accurate x ray diagnosis) Even when ova are absent from the stools, both dead and viable ova have been found in the rectal biopsy material

Skin (I) (301, 305) (T-652)

Technical Notes Representative sections are important particularly at the margins of typical active lesions Differential stains and multiple biopsies are often indicated Lesions should not be selected from the leg when searching for pigmentary or vascular findings A superficial biopsy will not demonstrate changes deep in the corium

A rotary drill punch is now being used in many quarters to obtain skin biopsies It is of special value in children because of the little pain associated with the procedure Multiple sites must be biopsied from large lesions—such as a large ulcer at the site of a long standing burn—when the possibility of malignant degeneration is being considered Inasmuch as no anesthesia is required and there is little hazard of the dissemination of cancer cells with the technique, the use of the rotary punch drill has proved of considerable value in both the biopsy of cutaneous tumors before x ray therapy and for obtaining serial histologic or histochemical studies of the skin (328) The skin can be biopsied at precise depths ranging from 3 to 8 mm The only precautions of note that must be exercised concern areas wherein the supporting tissues might be too resilient for proper punch action, such as those over major vessels in the skin over bony or cartilaginous prominences or in areas that are close to the eye

The specimen should not be removed with forceps or by squeezing Procaine should be injected around (but not into) the lesion

With reference to scleroderma biopsies are often inadequate because superficial portions of the dermis are excised from far removed sites for healing and cosmetic reasons It is important for the pathologist to be familiar with the considerable variation in the amount and appearance of collagen bundles in the skin from different regions of the body if he is to avoid diagnostic error

In the presence of a lesion that is probably lupus erythematosus the biopsy should be taken from the most active area of the plaque Since such a biopsy must be sufficiently deep it is best obtained from the scalp or some other cosmetically unimportant part

Clinical Clues May be diagnostic in the cutaneous lymphomas, collagen disorders metastatic neoplasms thrombohemolytic thrombocytopenic purpura hemochromatosis lupus vulgaris leprosy, the cutaneous mycoses, xanthomatosis the histiocytic reticuloendothelioses and in the evaluation of nevi (intradermal compound or junctional)

The histopathologist may be able to differentiate between discoid lupus erythematosus and the disseminated form In the former the collagen is little affected and there is liquefaction degeneration in the region of the epidermal-dermal junction

Skin (II)

Technical Notes Suspicious areas such as the lip and vulva, can be scraped with a wooden spatula The tissue so obtained should be fixed immediately in ether alcohol

CLINICAL CLUES While this technique may be diagnostic it should not replace the formal biopsy of a suspicious lesion when the latter is indicated

Spleen (303) (T-734b, 737, 738)

TECHNICAL NOTES The splenic puncture is performed during expiration with a Vim-Silverman needle A point of entry is chosen between the upper and lower borders of percussion The specimen is fixed in formaldehyde-Zenker s solution This technique is contraindicated in the presence of a hemorrhagic tendency and a nonpalpable spleen A nodular mass of white pulp which has been smeared out should not be mistaken for lymphatic leukemia

Biopsy of the spleen by means of a Vim-Silverman needle is potentially very dangerous since it may be followed by a fatal splenic rupture Accordingly splenic aspiration is preferable Only 0 1 to 0 2 ml of splenic "juice ' need be aspirated and processed Splenic puncture via the thorax should never be attempted if it can be avoided

Hemorrhagic complications might be averted in patients with enlarged spleens who have thrombocytopenia by the prior administration of a plastic bag transfusion of fresh blood

Shields and Hargraves have set forth the following normal ' splenogram findings based on the counting of 5000 nucleated cells from such aspirations lymphocytes—70 per cent (65 per cent mature, 4 8 per cent reticular or immature), granulocytes—25 per cent (22 7 per cent segmented 1 5 per cent bands 0 6 per cent eosinophils, 0 2 per cent basophils, and very few cells younger than metamyelocytes), monocytes—2 5 per cent, and less than 2 5 per cent endothelioid cells histiocytes, macrophages, plasma cells, Turk cells, and pulp cells (303b) They point out that the finding of over 90 per cent lymphocytes is *not* necessarily diagnostic of a lymphocytic lymphoma

CLINICAL CLUES May be diagnostic in an unexplained case of splenomegaly, particularly when due to myeloid metaplasia the lymphomas, kala azar, the leukemias, the primary lipoidoses, and the infectious granulomas

Subcutaneous Nodules (322)

TECHNICAL NOTES Suitable nodules should be searched for particularly over the extensor surfaces and along the back One must not confuse chondrodermatitis nodularis chronica helicis of the auricle with a tophus

CLINICAL CLUES May be diagnostic for rheumatic fever or rheumatoid arthritis, except when the rheumatoid nodule is very early or when the rheumatic nodule is long standing The rheumatoid lesion is larger has more sharply defined necrotic zones and more fibrosis than its rheumatic counterpart Similar nodules may be seen in patients with disseminated lupus erythematosus and scleroderma who exhibit a rheumatoid like arthritis

Synovial Membrane (322, 326)

TECHNICAL NOTES The punch biopsy technique of the affected joint capsule is best performed on the knee A specially devised trocar is inserted into the suprapatellar pouch after which a tubular cutting needle is introduced The synovial surface is more clearly delineated by distending the space with saline, while an elastic bandage is applied over the lower portions of the knee Open biopsy under local anesthesia yields a greater proportion of successful results, however

There may be major variations in the histologic character of the synovial lesions

even in different portions of the same joint If gout is suspected, the tissues should be fixed in absolute alcohol (rather than aqueous fixatives) in order to preserve the water-soluble needle-like crystals of the acid urates Urates may be demon strated with de Galantha s stain

CLINICAL CLUES May be diagnostic of obscure inflammations, infections neoplasms degenerative processes or collagen disorders affecting one or many joints No precise basis exists at present for distinguishing the rheumatoid lesions from those observed in the dyscollagenoses and in certain chronic infectious arthritides (especially brucellosis) Gout has been accurately diagnosed in the majority of acute cases by the finding of urate crystals in the synovial tissues (326) The gross and histologic features of pigmented villous synovitis are quite char acteristic

Temporal Artery (T–810, 811)

TECHNICAL NOTES Excisional biopsy of the affected segment can be readily performed

CLINICAL CLUES This procedure has proved to be both diagnostic and curative of temporal arteritis Steroid therapy need not be withheld until a biopsy is performed particularly if the vision is progressively deteriorating

Testes

TECHNICAL NOTES See Studies of Endocrine Function (p 729)

CLINICAL CLUES Very valuable in the evaluation of hypogonadism cer tain cases of sterility and testicular masses

Thyroid Gland (310)

TECHNICAL NOTES After local procaine infiltration the Vim Silverman trochar is introduced tangentially to the trachea up to a point against the thyroid gland The split needle is then inserted its full length into the gland s substance and rotated Following removal local pressure is applied

CLINICAL CLUES This technique is most helpful in differentiating the various types of chronic thyroiditis from nodular goiter short of surgery Prior to its use the correct preoperative diagnosis was made in only 17 5 per cent of 114 cases of Hashimoto s thyroiditis at one clinic (315)

Tophus (Suspected)

TECHNICAL NOTES Sodium urate crystals can be demonstrated by smear (as long needle crystals) or by the murexide reaction Biopsy specimens should be fixed in absolute alcohol

CLINICAL CLUES May confirm the presence of long standing gout (One should remember that xanthomas of tendons may clinically resemble tophi) Biopsy of a tophus will distinguish this lesion from the subcutaneous nodule of rheumatoid arthritis

SECTION XII

Supplementary X-ray and Photographic Procedures (329)

Chest Films (236, 240, 241, 268, 269)

TECHNICAL NOTES Good technique is very important (One should be able to make out the intervertebral spaces in the P A view) Standard films can be supplemented by lateral oblique, lordotic (255) lateral recumbent,(279) stereoscopic, and other views as indicated They may be further supplemented by bronchography, spot films, and overexposed Bucky films They should be repeated frequently if an evolving process is suspected The silhouette sign has proved to be most helpful in localizing intrathoracic lesions from the posteroanterior roentgenogram (250) (Also see Section IX, p 781)

CLINICAL CLUES A basic diagnostic necessity for detecting disease of the heart lungs pleura, ribs, diaphragm mediastinum, and thoracic vertebrae These films may also occasionally indicate lesions in the neck, shoulder girdle spleen, stomach (through the gas bubble) and liver A hiatal hernia may be detected in the plain film (263) The finding of a very small heart should make one suspicious of Addison s disease (333)

"Metastatic Series"

TECHNICAL NOTES The long bones pelvis spine, chest and skull are usually the most important sites to survey

CLINICAL CLUES The study of such widespread structures is necessary in atypical cases of Paget s disease, myeloma fibrous dysplasia and eosinophilic granuloma of bone It is also essential in the follow up of certain malignancies, particularly those of the breast lung kidney thyroid, and prostate Multiple myeloma, Paget s disease, hyperparathyroidism, and chronic uremia can affect other bones of the body apart from the ribs spine and pelvis Certain malignancies such as neuroblastomas have rather characteristic appearances when they metastasize to bone (p 333)

Tomography

TECHNICAL NOTES Various organs and lesions in the chest abdomen and skull can be more readily delineated by this method of radiographic dissection It should be employed judiciously since it is not only a costly and complicated

procedure but also necessitates the delivery of a large amount of radiation to the patient

CLINICAL CLUES This technique may be very useful in identifying lung cavities and calcifications calcification of the pericardium and heart valves, kidney tumors, and brain lesions (276)

Retroperitoneal Pneumography

TECHNICAL NOTES This is a relatively simple technique that is performed by the injection of air or oxygen (about 800 cc) into the areolar tissue of the presacral area

The presacral route of retroperitoneal pneumography has not abolished the possible dangers of gas embolism Furthermore oxygen is no safer than air Carbon dioxide is apparently the only safe gas for retroperitoneal pneumography (131) (T-1296) (The safety of *pure* carbon dioxide—which is 20 times as soluble in serum as is air or oxygen—is pointed out by the lack of untoward effects when up to 100 cc of this gas are injected intravenously into humans for contrast visualization of the intracardiac structures)(242)

CLINICAL CLUES This study has proved very helpful in the delineation of adrenal and retroperitoneal tumors Retroperitoneal masses are also apt to displace the ureters obliterate the iliop oas shadow displace the gastric air bubble laterally, and displace the second portion of the duodenum anteriorly (especially right adrenal tumors) (118) They do not descend when the patient stands

Several sources of confusion in the interpretation of presacral air studies include the fundus of the stomach visualized 'on end and an enlarged spleen being mistaken for an enlarged left adrenal gland The duodenum may produce a similar but smaller density on the right side (331) Another potential source of error is the demonstration of an enlarged adrenal which ultimately proves to be a benign nonfunctioning adrenocortical tumor

Diagnostic Pneumoperitoneum (342)

TECHNICAL NOTES A pneumoperitoneum is induced in the usual manner following local anesthesia and a careful check that the air is actually being introduced into the peritoneal cavity The induced shoulder pain can usually be controlled with oral codeine Approximately 350 to 500 cc of air is injected

CLINICAL CLUES This study may aid in the diagnosis of disease within the diaphragmatic area In addition to the diaphragm itself the following organs may be visualized—esophagus stomach, spleen kidneys liver, and adrenal glands Lesions that may be properly identified include eventration of the diaphragm herniation of the stomach an enlarged spleen (often mistaken for an enlarged adrenal) (p 22), pancreatic cysts and tumors and calcified densities in the liver (especially echinococcal cysts) Diagnostic pneumoperitoneum can be of considerable aid in delineating the nature of lesions noted at the right cardiophrenic angle in the P A chest film Pneumoperitoneum has also been advocated as a therapeutic diagnostic test when the relationship of chest pain to a hiatal hernia is not clear (p 810)

Teeth (340)

TECHNICAL NOTES Physicians should not be reluctant to examine the teeth either clinically or by x ray Dental development may be of value in determining the age of children

CLINICAL CLUES Absence of the lamina dura has been noted in the Cush

ing syndrome osteomalacia hyperparathyroidism scurvy, surgical menopause in young women and occasionally in Paget s disease of the bone Other changes affecting the teeth and gums are at times conspicuous in hyperparathyroidism, hypoparathyroidism hypopituitarism hyperthyroidism, hypothyroidism, the adrenogenital syndrome, polyostotic fibrous dysplasia, progeria, juvenile diabetes and porphyria One should look for periodontal suppuration in cases of unexplained hectic fever particularly around the deciduous teeth in children (T-384)

Pelvis (Blood Vessels and Seminal Vesicles)

TECHNICAL NOTES Abnormalities of these structures may be incidentally noted in films taken for other indications

CLINICAL CLUES Premature calcification of either structure is suggestive of diabetes mellitus

Bone Structure (330, 332)

TECHNICAL NOTES All of the pathognomonic signs of malignancy have been mimicked by other benign or developmental conditions, particularly in children (T-1155) Any single lesion should be studied from more than one angle At least 30 per cent of the calcium must be lost from bone before the loss is detectable With the exception of the calvarium, the finding of new bone formation perpendicular to the long axis of a bone is highly suggestive of malignancy in the case of a suspected bone tumor

CLINICAL CLUES The altered bone reaction to infection that is produced by chemotherapy and the antibiotics often simulates neoplastic and other disorders (329) One cannot diagnose osteoporosis, osteomalacia or osteitis fibrosa generalisata on the basis of bone density alone Unexplained osteoporosis should alert the clinician to the diagnosis of hyperparathyroidism hyperthyroidism, the Cushing syndrome hemolytic anemia, myeloma sprue and the Fanconi syndrome The pseudofractures (Looser s zones) in osteomalacia are due to the pressure by the adjacent blood vessels (T-80)

Leukemia usually involves the bones only in children (341) Sarcomatous degeneration should be suspected in Paget s disease of the bone when subcortical bone lysis with rapid soft-tissue growth is noted (T-1010)

Bone x rays may help to indicate various poisonings, particularly when caused by lead and vitamin A or D intoxication The demonstration of a central nidus surrounded by a sclerotic zone over a painful area of bone in young people is suggestive of an osteoid osteoma

Femora

TECHNICAL NOTES Routine x rays of these bones

CLINICAL CLUES Both the characteristic flask shape and flattening of the head are occasionally observed in Gaucher s disease (T-287) Aseptic necrosis of the head is noted in the sickle cell hemoglobin C and the sickle cell thalassemia syndromes and less frequently in pure sickle cell anemia (T-715-717)

Bones of the Hands and Feet

TECHNICAL NOTES Routine x rays of these areas

CLINICAL CLUES These bones are commonly affected by sarcoidosis but rarely by tuberculosis and the other granulomata (T-746) Hypertrophic osteoarthropathy may be the first clinical manifestation of malignancy (T-1037 1039)

Amorphous deposits at the tips of the fingers—with or without resorption of the bone—are strongly suggestive of chronic nephritis with a secondary hyperparathyroidism A subperiosteal resorption particularly along the margins of the phalanges, is noted in hyperparathyroidism and renal osteodystrophy, but not in the other metabolic bone disorders (T-76)

Eyes

TECHNICAL NOTES The bone-free technique with standard dental films is used Several tangential films are centered toward the external canthus and taken from behind with the eyes open

CLINICAL CLUES A band keratopathy and conjunctival crystals due to hypercalcemia are noted in the milk alkali (Burnett) syndrome hyperparathyroidism and vitamin D excess (T-314)

Salivary Glands (T-1220d)

TECHNICAL NOTES The radio-opaque material is usually injected with relative ease in the Mikulicz disease especially in the advanced stages This contrasts with the pain that is apt to be produced by the introduction of amounts as small as 0 5 ml in the Mikulicz syndrome (due to the readiness with which the capacity of the duct system can be reached) The degree of emptying following salivary stimulation is an index of salivary glandular function This can be determined by taking serial films at 5 minutes 30 minutes 1 hour and 24 hours

CLINICAL CLUES Sialography may help in the differentiation of the Mikulicz syndrome (resulting from involvement of the tissues by leukemia lymphoma sarcoidosis tuberculosis or other systemic disorders) and the Sjogren Mikulicz disease In the latter condition there is primarily a sialectasis or terminal duct dilatation which may be encountered in one of four stages (viz the punctate stage the globular stage the cavitary stage and the destructive stage) The swelling can be unilateral or bilateral In the case of the Mikulicz syndrome the pathologic changes in the lymph tissue tend to displace the parotid gland but the glandular architecture remains unaltered until late infiltration has taken place

The size of the salivary gland often shows little correlation with the sialographic picture It is wise to establish the definitive diagnosis by a surgical biopsy In the Sjogren Mikulicz disease the retention of the contrast medium in the terminal ducts is due to the inability of the secretory pressure within the acini to overcome the resistance offered by the narrowed interstitial or septal ducts In the end stages of this disorder the material can remain for days to weeks once the gland septa are permeated

Pinna of the Ear

TECHNICAL NOTES Usually recognized on routine lateral films of the skull

CLINICAL CLUES Calcification is often associated with prolonged DOCA therapy in Addison s disease Actual metaplastic ossification has even been noted (333)

Soft Tissues

TECHNICAL NOTES Usually best observed in relation to the adjacent bone and joint structures

CLINICAL CLUES Periarticular calcification may be noted in vitamin A and D excess (T-1173 1176) Involvement of the soft tissues by calcinosis hypercalce-

mia from various causes and metastases may be seen if looked for Obliteration of the cervical fat interfascial spaces by a metastatic carcinoma has occasionally been diagnosed by an alert radiologist The decreased density of fat tumors may indicate the nature of a perirenal tumor

Infrared Photography

TECHNICAL NOTES An infrared photographic technique which penetrates approximately 2 5 cm, employing an incandescent tungsten filament, a Wratten #87 filter, and infrared sensitive film is employed

ABDOMINAL WALL

TECHNICAL NOTES One may also be able to see the collateral channels well with polaroid dark adaptor x ray goggles In addition, the direction of blood flow may be observed (337)

CLINICAL CLUES The development of widespread anastomoses involving the veins in the abdominal wall indicates prolonged portal hypertension, as occurs in cirrhosis, the Banti syndrome and a chronic Budd Chiari syndrome (334) They *are not found in acute hepatitis fatty infiltration or carcinoma of the liver* These collaterals are also useful in diagnosing obstruction of the inferior vena cava

CHEST WALL AND BREASTS

TECHNICAL NOTES The value of this technique may be enhanced by a correlation with phlebography and venous pressure studies (335)

CLINICAL CLUES A graphic demonstration of the extensive collateral circulation in obstruction of the superior and inferior vena cavae can be obtained in this manner A wide variation in the venous pattern of the breast occurs both normally and in disease states

Wood Light Fluorescence (336)

TECHNICAL NOTE Employed over skin tumors or areas of alopecia

CLINICAL CLUES A vivid reddish-orange fluorescence has been noted in epidermoid carcinoma (squamous cell epithelioma) and in other highly malignant ulcerated, or necrotic neoplasms It is also of value in selecting proper biopsy sites in such instances and in the diagnosis of ringworm of the scalp

SECTION XIII

Studies of the Eyes in Systemic Disorders

Visualization of the Anterior Eye Tissues, Pupils, and Lenses (349)

TECHNICAL NOTES *Direct observation ophthalmoscopy and the use of* the slit-lamp illumination technique are all valuable

CLINICAL CLUES These procedures may aid considerably in the diagnosis of the following systemic disorders

1 The multiple germ cell dysplasias (Werner Rothmund)—juvenile cataracts with starlike opacities (not found in the ectodermal dysplasias) (p 419) (T–1227)

2 Arachnodactyly—subluxation of the lens (p 425)

3 Hepatolenticular degeneration (Wilson s disease)—the Kayser Fleischer ring (p 101) (T–363 364)

4 Hypoparathyroidism—cataracts of the cortical type (may develop as early as 2 to 6 months) (p 27) (T–81)

5 Hypercalcemia due to various causes (hyperparathyroidism the milk alkali syndrome sarcoidosis vitamin D excess)—band keratopathy and conjunctival crystals (T–314) Also see Section XII (p 82) and Figure 47 (Atlas page 29)

6 Diabetes mellitus—senile-type cataracts (344)

7 Congenital anomalies due to rubella—congenital cataracts

8 Hyperthyroidism—exophthalmos retraction of the upper lids

9 Infections (tuberculosis syphilis brucellosis)—conjunctivitis iridocyclitis chorioretinitis

10 Gaucher s disease—pingueculae (p 78)

11 Neurodermatitis—a characteristic shield like cataract

12 Chronic obliteration of the great arterial trunks—cataracts iris atrophy, corneal opacities (p 301) (T–918-921)

13 Myotonia dystrophica—fine dustlike subcapsular deposits which appear scintillating and colored under the slit-lamp (may be diagnostic) (p 421) (T–1235)

14 Cystinosis—cystine deposits in the cornea and conjunctiva (p 57) (T–197)

Fundal Examination (Discs, Retinae, Blood Vessels) (351, 353)

TECHNICAL NOTES Visualization of the entire fundus of both eyes should be a *routine* part of the complete physical examination Mydriatics and considerable patience with hypersensitive patients are often very rewarding A careful search for the following should be made in patients suspected of having the diseases listed under Clinical Clues exudates hemorrhages retinal inflammation

edema, or "sheen" (a wet glistening appearance of the entire retinae—particularly important in the toxemias of pregnancy) lipemia proliferation, hemangiomas papilledema and angiosclerosis

The correct identification of drusen bodies, anomalous retinal vessels, and myelinated nerve fibers is highly important in order to avoid confusing these common and benign anomalies with papilledema (T-1107c) Similarly one should be able to differentiate an optic neuritis from papilledema (T-1107b) One must not confuse medullated nerve fibers or the degenerative drusen bodies for exudates Changes in hypertensive disease should be interpreted very cautiously when the patient is receiving therapy

The clumping or sludging of blood in the retinal veins when pressure is applied to the upper eyelid (just firmly enough to produce a partial diastolic collapse of the retinal arteries but without actually distorting the eye) may be indicative of systemic organic disease (354) When the test is positive one observes a granular appearance to the blood in these veins, followed within 5 to 8 seconds by the formation of large discrete particles

CLINICAL CLUES May be extremely valuable in the diagnosis, prognosis and management of the following systemic disorders

1 Diabetes mellitus—the retinal microaneurysms in diabetics appear as tiny, round red dots They may occur singly or as a cluster at the end of a small vessel (actually the venous end of the capillaries) These aneurysms are usually found either in the periphery of the fundus or in the posterior pole They are just within the limits of visual acuity measuring 30 to 60 microns in diameter (343)

2 General arteriosclerosis (344)

3 Hypertensive cardiovascular disease (344)

4 Acute and chronic kidney failure

5 The toxemias of pregnancy (348)

6 Toxoplasmosis (p 172) (T-633 634)

7 The Laurence Moon Bardet Biedl syndrome (p 421) (T-1233)

8 The von Hippel Lindau disease (p 382) (T-1142)

9 Multiple sclerosis (p 356) (T-1053)

10 Temporal arteritis (p 222) (T-810, 811)

11 Cerebral fat embolism—oval fat masses in the retinal vessels and subhyaloid hemorrhages (p 216) (T-792)

12 Lupus erythematosus—retinal cytoid bodies (p 305) (T-928)

13 Elastica disease (the Gronblad Strandberg syndrome)—angioid streaks and other retinal alterations (p 314) (T-985)

14 Subarachnoid bleeding—hemorrhages with a red halo

15 Lignac Fanconi disease—retinitis pigmentosa (p 57) (T-195b)

16 Refsum s syndrome—retinitis pigmentosa (p 381) (T-1138)

Capillary Microscopy

TECHNICAL NOTES The blood vessels and circulating blood in the bulbar conjunctivae from the limbus to the outer angle may be studied with the stereoscopic dissecting microscope (a range magnifying power from 16 to 150 times) Illumination by a Shahan ophthalmic lamp is also required

CLINICAL CLUES This network is both anatomically and embryologically related to the vascular system of the subcutaneous tissue in other parts of the body It can give considerable information about predisposition to diabetes mellitus, (347) diabetic complications and even rheumatic fever (346) Hemodynamic changes (i e the degree of vasoconstriction reactivity to epinephrine and the coiling tortuosity and elongation of the capillaries and venules) differ in essential hypertension and pheochromocytoma (350)

Visual Field Studies (352)

TECHNICAL NOTES The results of careful perimetry can define lesions and defects that are not demonstrable by performing the test grossly with the fingers A series of graded test objects may be necessary to determine the depth of loss in the defective region and the quality of the preserved field

CLINICAL CLUES A bitemporal hemianopia in a problem case of hyper tension thyroid disorder, diabetes mellitus arthritis, amenorrhea, and impotence may point to an underlying pituitary tumor A right lateral homonymous hemi anopia *due to a cerebral vascular occlusion or brain tumor usually causes much* less disturbance than comparable defects on the left side

Extraocular Muscle Function

TECHNICAL NOTES A careful study of the eyeball motions in all spheres of its movement is made

CLINICAL CLUES Partial or complete palsies may be indications of hyper thyroidism, hypothyroidism myasthenia gravis primary or metastatic brain *tumors, and central nervous system syphilis*

Test for Lacrimal Secretions

TECHNICAL NOTES A strip of litmus or filter paper is bent 5 mm from the end and the short end hooked onto the lower lid just lateral to the inferior punctum Double acid washed Whatman No 41 filter paper is recommended

CLINICAL CLUES Keratoconjunctivitis sicca is a manifestation of a sys temic disorder (the Sjogren syndrome) (p 414) (T-1219 1220) Deficient tearing *is present if at least 10 to 15 mm of paper is not moist after five minutes*

The most frequent identifying feature of dysautonomia is the absence of lacri mation (crying without tears) (p 381) (T-1140)

Glaucoma Suspect

TECHNICAL NOTES If the initial levels are not conclusive, tonometric readings may be taken in a series (three or four in an hour) after the patient drinks 1000 ml of water (344)

CLINICAL CLUES *A 10 mm* rise in the intraocular *pressure indicates prob-* able wide-angle glaucoma This may be quite helpful when an iritis is also being considered

Retinal Artery Pressure Determination

TECHNICAL NOTES A Bailliart ophthalmodynamometer, which measures pressures from 10 to 150 gm of water is applied to the lateral surface of the sclera Mydriatics are used but local anesthesia is not necessary Several readings of both the systolic and diastolic pressures are obtained with the patient in the supine position Ophthalmodynamometry has the obvious advantage of safety over arteriography and digital pressure when a stenosis or occlusion of the carotid artery is suspected

CLINICAL CLUES Significantly lower pressures in the ipsilateral eye are obtained in patients with both partial and complete occlusion of the internal carotid artery (T-1092b)

SECTION XIV

Therapeutic Diagnostic Tests

CARDIOVASCULAR DISORDERS

Pneumoperitoneum Trial (367)

TECHNICAL NOTES A pneumoperitoneum is instituted (usually with 500 cc of air) followed by refills as often as is needed to ascertain the relationship of a hiatal hernia to angina pectoris

CLINICAL CLUES The prompt cessation of angina in the presence of a large sliding type esophageal hiatal hernia (due to the displacement of the hernia by air) may not only establish its relationship to the pain but can aid in evaluating and recommending hernioplasty for prolonged relief

Carotid Sinus Pressure Trial (361)

TECHNICAL NOTES Unilateral pressure is exerted over the carotid bifurcation for 10 to 15 seconds with the patient sitting upright The patient should count aloud If available electrocardiographic control must be used when a rhythm disorder is present

CLINICAL CLUES The clinical and electrocardiographic response may be diagnostic of auricular flutter and paroxysmal auricular tachycardia This maneuver may stop an attack of angina pectoris (even when not due to an associated rapid heart action) by interrupting either the sympathetic reflex arcs or the sensory pathways

This is also a valuable technique in the differentiation of gallop rhythm from other types of triple rhythm Whereas the true gallop sound invariably becomes inaudible when the ventricular rate is made slower than 91 per minute, the other types of extra sounds usually become more obvious because of the changes in timing intensity or clarity

Diuretic Trial

TECHNICAL NOTES A course of diuretic therapy with or without digitalis, is administered in the presence of heart disease and a recent unexplained "lung tumor" particularly if the latter is found in the right midlung field Diuretics should also be tried in the presence of an unexplained high fever following a myocardial infarction

CLINICAL CLUES The so-called vanishing tumor of the lung is caused by a localized interlobar pleural effusion in congestive heart failure (T-832e) It usually promptly disappears following diuresis thus obviating further medical or

surgical diagnostic approaches for a suspected carcinoma The right transverse fissure is most often the site of such a tumor *The fever due to interstitial pulmonary edema often will promptly subside after diuresis* (T–452)

Regitine Test (T–62, 64)

Technical Notes 5 mg of Regitine are injected intravenously after accurate baseline blood pressure levels have been obtained False-positives occasionally occur when azotemia is present or if sedatives and antihypertensive drugs are not discontinued False-positive tests with Regitine can occur as long as four weeks following the cessation of Rauwolfia therapy (p 22)

Clinical Clues A decrease in blood pressure of 35/25 within several minutes is highly suggestive of a pheochromocytoma

CENTRAL NERVOUS SYSTEM DISORDERS

Neostigmine Trial

Technical Notes A dose of 1 or 2 mg is administered intramuscularly

Clinical Clues Dramatic improvement in the patient s appearance speech and swallowing occurs within several minutes if myasthenia gravis is present Some nonspecific improvement may be noted in certain of the myopathies, such as amyotrophic lateral sclerosis (p 373)

Edrophonium Chloride (Tensilon) Trial (369, 375)

Technical Notes 1 ml (10 mg) of edrophonium chloride is placed in a tuberculin syringe If no reaction occurs within 30 seconds after 0 2 ml (2 mg) is given intravenously the remaining 0 8 ml is injected If a cholinergic reaction occurs with 0 2 ml the test is discontinued A placebo control is employed if the possibility of a psychoneurosis exists

Clinical Clues May be diagnostic of myasthenia gravis (as evidenced by a temporary increase in muscle strength and general subjective improvement within the first 2 minutes) It may also be diagnostic of a cholinergic crisis due to overdosage Tensilon is much safer than neostigmine in this regard because of the short duration of its action (Also see Group XII of Part I, p 371)

Antiepileptic Trial

Technical Notes Various antiepileptic drugs are administered depending on the type of seizures suspected (grand mal, petit mal and psychomotor equivalents)

Clinical Clues Helpful in evaluating the atypical epileptic variants particularly when they result in abdominal autonomic and myoclonic paroxysms

THE ENDOCRINOPATHIES

Lugol's Solution Trial

Technical Notes 10 drops t i d is a very adequate dose

Clinical Clues The prompt clinical improvement may be diagnostic in atypical cases of hyperthyroidism

Antithyroid Trial

TECHNICAL NOTES Propylthiouracil in doses of 300 to 400 mg daily is usually adequate Tapazole and other related compounds can also be employed

CLINICAL CLUES A positive clinical response (viz, lowering of the basal metabolic rate improvement of heart failure, and a rise in the serum cholesterol) occurs within several weeks in atypical cases of hyperthyroidism The failure of hyperthyroid like symptoms to abate should suggest other causes, such as a pheochromocytoma

Thyroid Trial (I) *(355, 360)*

TECHNICAL NOTES Only small amounts of thyroid are necessary (usually *not more than 60 to 120 mg daily) One should check for associated changes in the cholesterol basal metabolic rate and electrocardiogram voltage*

CLINICAL CLUES A characteristic response of great discomfort followed by improvement ensues in 1 to 2 weeks if the patient is truly hypothyroid The cholesterol will drop in hypothyroidism, even if the level is relatively normal before therapy When thyroxine is given as a single intramuscular dose (2 mg) in children, the cholesterol will remain low for one month if hypothyroidism is actually present

Thyroid Trial (II) (371)

TECHNICAL NOTES The I^{131} uptake is measured before and two weeks after ingestion of 180 to 200 mg thyroid extract daily A decrease of more than 30 per cent from the initial iodine uptake occurs in 95 per cent of euthyroid subjects

CLINICAL CLUES A decrease of 30 per cent occurs in only 3 per cent of hyperthyroid patients because of their insensitivity to even large doses of thyroid extract (or triiodothyronine) In half of the patients with hot' and solitary nodular goiters however the active nodule fails to be inhibited

Cortisone Suppression Trial (T–91, 92)

TECHNICAL NOTES 100 mg of cortisone acetate is given intramuscularly daily The urinary 17 ketosteroid levels are followed

CLINICAL CLUES The ketosteroids tend to fall significantly if the adrenogenital syndrome is due to bilateral hyperplasia of the adrenal cortex No change is usually noted if malignancy of the adrenal cortex is present Experience has shown however, that even though cortisone or its analogs may suppress the adrenal s activity in a patient with the Cushing syndrome a tumor cannot always be ruled out

Pitressin Trial (111, 145)

TECHNICAL NOTES 0 1 unit of Pitressin is injected intravenously It may be performed in conjunction with the saline test (p 722)

CLINICAL CLUES The diuresis is promptly inhibited in true diabetes insipidus This test helps to differentiate this disease from renal polyuria and from primary aldosteronism

DRUG INTOXICATIONS

Atropine Trial (363)

TECHNICAL NOTES Atropine sulfate is administered intravenously or intramuscularly in doses of from 2 mg (1/30 gr) up to 6 mg (1/10 gr) in the presence of severe muscarinic manifestations

CLINICAL CLUES A prompt response usually occurs if reversible anticholinesterase intoxication is present (In its absence 2 mg will produce no serious effects) Treatment should be continued vigilantly until the effects of the toxin have been completely dissipated

Mecholyl or Pilocarpine Trial (356)

TECHNICAL NOTES Doses of 10 to 25 mg and 5 mg are injected intramuscularly respectively

CLINICAL CLUES The flush sweating bradycardia and other parasympathomimetic effects fail to appear if poisoning due to atropine and its related compounds is present

N Allylnormorphine (Nalline) Trial (366)

TECHNICAL NOTES Nalline is administered parenterally in severe respiratory depression when the possibility of opiate intoxication is present particularly if emphysema or asthma exists 10 mg is a safe exploratory dose, although as little as 1 mg and as much as 45 mg have been successfully used

CLINICAL CLUES A prompt response with marked improvement in respiration usually ensues if depression due to narcotic administration is present

INFECTIOUS DISEASES AND INFLAMMATIONS

Antiamebic Trial (374)

TECHNICAL NOTES Chloroquine diphosphate is administered (0 1 gm for 2 days and thereafter 0 5 mg for 21 days) orally or emetine hydrochloride (0 065 mg subcutaneously for 7 to 10 days)

CLINICAL CLUES Dramatic changes within 3 to 5 days in the temperature white count pain and liver tenderness and size may be noted if an amebic liver abscess is present

Antimalarial Trial (374)

TECHNICAL NOTES Chloroquine (Aralen) is administered (1 0 gm followed by 0 5 gm in 6 hours and 0 25 gm daily for several days) Amodiquin (Camoquin) or quinacrine (Atabrine) may also be employed

CLINICAL CLUES A prompt cessation of the fever and chills ensues if they are due to malaria

Chloroquine (Aralen) or Quinacrine (Atabrine) Trial (T-940)

TECHNICAL NOTES Daily doses of 250 to 500 mg and 200 to 400 mg respectively are administered orally

CLINICAL CLUES A good response of the erythema and inflammatory infiltrate usually ensues within several weeks in chronic discoid lupus erythematosus

Potassium Iodide Trial

TECHNICAL NOTES A saturated solution may be given in doses of 10 drops t i d to a patient exhibiting fever in the presence of a positive serology

CLINICAL CLUES The prompt normalization of fever in such an instance is highly suggestive of latent or tertiary syphilis—even more so than a similar response to penicillin

Penicillin Trial (T–553)

TECHNICAL NOTES 10 million units of penicillin are given intramuscularly over 7 to 10 days

CLINICAL CLUES A Herxheimer reaction may ensue shortly after the first few injections in active syphilis If fever is caused by tertiary syphilis, it should promptly subside A suspected solitary gumma will usually disappear or resolve considerably on this regimen

Salicylate Trial (T–972)

TECHNICAL NOTES Ingestion of adequate amounts of aspirin (0 6 mg or more every 4 hours) is necessary

CLINICAL CLUES The pancarditis, fever, and polyarthritis of rheumatic fever usually exhibit prompt defervescence on large doses of salicylates

NEOPLASMS

Nitrogen Mustard or Triethylene Melamine Trial (*357, 358*)

TECHNICAL NOTES Adequate amounts of nitrogen mustard (HN_2) must be given (a total of at least 0 4 mg per kg of body weight intravenously over a 1 to 7-day period) Triethylene melamine may be administered orally in an initial total dose of 10 to 15 mg

CLINICAL CLUES The cessation of a chronic unexplained fever is suggestive of a lymphoma, especially in the retroperitoneal area (p 184) This treatment may also induce a remission in systemic lupus erythematosus, particularly in the presence of renal damage with edema

X-Radiation Trial (*368, 373*)

TECHNICAL NOTES Small amounts of x ray (750 r) can be delivered to enlarged mediastinal nodes and the effect noted in 2 to 3 weeks A similar dose may be administered to the nasopharynx

CLINICAL CLUES A 25 per cent decrease in the lymph node size suggests the presence of radiosensitive reticuloendothelial tumors particularly Hodgkin s disease This test must not be done, however until *every* attempt has been made to achieve a histologic diagnosis without it (p 337)

Cortisone Suppression Trial (359, 370)

TECHNICAL NOTES A 5 to 7-day control period is required during which 24-hour urinary calcium determinations are obtained The patient s dietary calcium intake should not exceed 200 mg daily Cortisone acetate (100 to 200 mg) is then administered intramuscularly daily for 7 to 10 days and the urinary calcium measured

Clinical Clues This test is particularly valuable in patients with metastatic cancer of the prostate or breast who have already undergone a gonadectomy and are subsequently showing an exacerbation. When a decision concerning adrenalectomy is sought, a marked reduction of calcium output and an amelioration of symptoms by cortisone may preoperatively indicate the value of this procedure.

METABOLIC DISORDERS

Thiamine Trial (I) (362)

Technical Notes A dose of 25 to 50 mg. is given parenterally daily.

Clinical Clues A dramatic response is noted in the clinical picture, the circulation time and the heart size when beriberi heart disease is present. In alcoholics this disorder can be suspected clinically by a high-output type of failure, a fast circulation time and no response to digitalis.

Thiamine Trial (II) (T-355)

Technical Notes Massive doses are administered parenterally.

Clinical Clues A gratifying response to this therapy may be observed if the central nervous system phenomena in a chronic alcoholic are due to Wernicke's encephalopathy and not to ammonium intoxication or hepatic coma.

Ascorbic Acid Trial (I) (376) (T-142)

Technical Notes A dose of 300 to 1000 mg. is administered daily for 7 days.

Clinical Clues A prompt response in both the bleeding manifestations and symptoms—along with a rise of the blood ascorbic acid—ensues if scurvy is present.

Ascorbic Acid Trial (II) (365)

Technical Notes An intramuscular loading dose of 200 mg. in infants or 15 mg. per kg. of body weight in adults is given. The blood levels of ascorbic acid are checked before the test and 4 hours later.

Clinical Clues The level rarely exceeds 0.2 to 0.4 mg. per 100 ml. following this procedure in the clinically manifest scorbutic patient.

Nicotinic Acid Trial

Technical Notes A dose of 100 to 150 mg. is administered daily for several days.

Clinical Clues A prompt clinical response of the dermatitis, anemia, diarrhea, or mental symptoms (particularly delusions referable to the skin)(T-140)—whichever symptom predominates—confirms the diagnosis in a suspected case of pellagra.

Vitamin K Trial

Technical Notes The prothrombin time is closely followed after the parenteral administration of a water soluble vitamin K preparation. Only 5 to 10 mg. of the latter are actually required.

CLINICAL CLUES In the presence of a lowered prothrombin time and jaundice (without an associated frank malabsorption defect in the bowel) a significant rise in the prothrombin time suggests an obstructive process rather than primary hepatocellular disease The absence of a prothrombin response indicates that diffuse hepatocellular damage is probably present

Potassium Trial

TECHNICAL NOTES Adequate amounts of potassium salts are given either orally or intravenously (more than 40 mEq per liter intravenously should not be given)

CLINICAL CLUES The respiratory distress and the associated electrocardiographic changes due to hypokalemia—either after diabetic coma, or due to the loss of excessive potassium via the urine or bowels—will respond (T-293 290) This therapy may also reverse the renal insufficiency and muscle degeneration due to hypokalemia (T-298) It can be used to diagnose and abolish digitalis intoxication (T-831d) The nocturnal attacks of periodic paralysis (caused by the migration of potassium into muscle) will usually respond promptly to such therapy (pp 79 and 80) (T-299)

Colchicine Trial

TECHNICAL NOTES Colchicine is taken in 0 5 mg doses every hour until relief of the joint pain or the onset of side effects (nausea, diarrhea) ensues

CLINICAL CLUES Acute atypical arthritis in males promptly responding to this regimen is probably gout

Vitamin B_{12} (or Liver Extract) Trial

TECHNICAL NOTES Only small amounts are actually needed (15 microgm of B_{12} intramuscularly daily)

CLINICAL CLUES The diagnostic reticulocyte rise and a clinical remission will ensue in true pernicious anemia Remission of a suspected combined system disease may also occur if this disorder is present

Carotene Trial (T-152)

TECHNICAL NOTES Four capsules of carotene are ingested daily The plasma carotene levels are then followed

CLINICAL CLUES If moderate depletion of carotene (30 to 70 microgm per 100 ml) is due solely to dietary inadequacy the level rises to normal This is especially valuable in functional diarrhea In steatorrhea, however severe depletion exists and no significant rise occurs without other forms of therapy

Corticotropin Trial (T-322)

TECHNICAL NOTES Intravenous ACTH is administered daily over a period of 6 to 10 hours in doses of 20 to 40 units The effects upon clinical and laboratory jaundice and the liver function are observed

CLINICAL CLUES The prompt and striking improvement noted in patients with infectious or toxic intrahepatic obstructive jaundice and cholestasis (cholangiolitis) may obviate the need for exploratory surgery When given as described after a sufficient period of observation and inconclusive study, this procedure is

usually quite safe (p 94) The usefulness of the ACTH test in the diagnosis of jaundice is somewhat marred by the fact that significant drops in the serum bili rubin levels have occurred in patients with proved extrahepatic obstruction

Versenate Trial (372)

TECHNICAL NOTES The amount of iron in the urine is measured following a single intravenous infusion of 80 mg edathamil calcium disodium (Versenate) per kg of body weight

CLINICAL CLUES This test is considered positive for the presence of ex cessive iron stores (hemochromatosis) if during the 24-hour period following the injection the urine contains more than 2 mg of iron per liter

Glucose Trial

TECHNICAL NOTES Small volume of concentrated glucose solution are given intravenously Sugar by mouth may be ingested if the patient can swallow and absorb the medication

CLINICAL CLUES Hypoglycemia should be suspected in patients exhibiting bizarre and unexplained mental and neurologic features peripheral vascular col lapse or coma (p 20) (T-48) A prompt response to glucose administration usually ensues if it is present This complication must be borne in mind in congestive heart failure with liver engorgement and cardiac coma (T-61) Since there is no con stant correlation between the level of blood sugar depression and hypoglycemic manifestations this clinical therapeutic test might prove to be very rewarding

SECTION XV

Withdrawal Tests

METABOLIC-ENDOCRINE DISORDERS

Cessation of Thyroid Medication (382)

Technical Notes Thyroid hormone is discontinued after 2 to 4 weeks of therapy

Clinical Clues A recurrence of symptoms along with an associated significant rise of the serum cholesterol will ensue within 6 to 12 weeks in hypothyroidism This study is particularly valuable in childhood

Abstinence from Thyroid Hormone

Technical Notes Factitious hyperthyroidism should be suspected if symptoms persist after apparently adequate medical or surgical therapy (These patients may be ingenious in hiding their supplies)

Clinical Clues Amelioration of the hypermetabolism will ensue in factitious hyperthyroidism This diagnosis can be confirmed by the elevated urinary iodine levels and by the depressed I^{131} uptake of the thyroid gland (T-45)

Abstinence from Insulin

Technical Notes These patients are also ingenious in hiding their supplies of insulin

Clinical Clues No further hypoglycemic attacks will occur in factitious hyperinsulinism in the absence of exogenous insulin This diagnosis should be suspected in nurses and in relatives of diabetics who are exhibiting suggestive hypoglycemic symptoms These individuals are also prone to present themselves with factitious fever (T-360)

Abstinence from Eating

Technical Notes The blood sugar level should be checked after an over night fast the critical level being 50 mg per 100 ml

Clinical Clues The occurrence of a hypoglycemic attack induced in this manner aids in differentiating organic and functional hyperinsulinism (T-48, 50) A hypoglycemia also ensues when adrenal insufficiency is present

Abstinence from Water

Technical Notes The patient should be observed very carefully during the day over an 8 to 12 hour period (if possible) Urine volume and specific gravity should be checked

Clinical Clues This is an important aid in differenting diabetes insipidus from functional polydipsia (133) The urine volume decreases and the specific gravity rises if the latter is present (Also see Section V, p 721)

Abstinence from Sodium (The Cutler Power Wilder Test) (112)

Technical Notes The performance of this test is very exacting and it has therefore not proved very useful It should be performed *only* in a hospital with the patient under careful observation over 2½ days if Addison s disease is suspected since an adrenal crisis may be precipitated

Clinical Clues A low serum sodium and chloride, a high serum potassium and an excessive loss of sodium in the urine will occur in adrenal insufficiency

Abstinence from Milk and Alkali (380) (T–1177, 1178)

Technical Notes The serum calcium the nonprotein nitrogen and the soft tissues (seen by x ray) are followed on this regimen Aluminum hydroxide gel may be added

Clinical Clues Patients with the milk alkali syndrome (Burnett) will demonstrate reduction or disappearance of the hypercalcemia and azotemia, along with a possible reversal of the metastatic soft tissue calcification (p 406)

Abstinence from Galactose (Milk) (T–275)

Technical Notes This procedure is preferable to the potentially hazard ous galactose tolerance test when galactosemia is suspected

Clinical Clues The symptoms and features of galactosemia (mental retardation cataracts and hepatosplenomegaly) will regress or disappear on this regimen (p 75)

Abstinence from Fat (T–283)

Technical Notes Determinations of the blood lipids are performed in patients with lipemic serum who are suspected of having familial hyperlipemia These analyses are instituted before and 30 to 90 days after rigid fat restriction

Clinical Clues If the lipid levels have not returned to normal within 1 or 2 months it is probable that another cause for their elevation exists such as renal disease diabetes mellitus chronic pancreatitis or hypothyroidism

Phosphorus Deprivation Test (T–69b)

Technical Notes After an initial period of observation, the patient is placed on a special low phosphate diet which may be supplemented by the ingestion of 30 ml of Basaljel with each meal The serum calcium and phosphorus are then studied and also the tubular reabsorption of phosphate if possible

Clinical Clues This test may help to establish conclusively the diagnosis of *hyperparathyroidism when the serum chemical analyses are equivocal* Whereas the normal individual is able to conserve phosphate over short periods of time after being deprived of this substance, this conservation mechanism does not func-

tion in the patient with hyperparathyroidism Accordingly, the phosphate loss will continue in this disorder even under the conditions imposed by the phosphorus deprivation

The normal phosphorus reabsorption index ranges from 0 58 to 0 96 An index of 0 86 or less occurs in hyperparathyroidism, hypercalcemia from other causes, and the secondary hyperphosphaturias Some investigators prefer that the phosphorus intake be only moderately reduced

The greatest value of the phosphorus reabsorption index may be as a screening test in normocalcemic patients with urolithiasis who are suspected of having hyperparathyroidism (even when the 24 hour excretion of calcium is not elevated) The same applies in the presence of unexplained bone disease (particularly atypical "Paget s disease) intractable peptic ulcer and in the relatives of patients with a parathyroid adenoma This test can also serve to diagnose unsuspected renal tubular acidosis

The value of the test is limited by the fact that there may also be diminished reabsorption of phosphorus from hypercalcemia of other causes and because of renal disease

HYPERSENSITIVITIES

Abstinence fom Gluten Ingestion (T-157)

TECHNICAL NOTES Numerous foods contain gluten particularly wheat and rye products

CLINICAL CLUES If the patient is sensitive to gluten or its metabolic degradation products, as in nontropical sprue and various allergies this may stop the steatorrhea—even after the vitamins, other allergic therapies and the steroid hormones have proved ineffective

Elimination Diet (Andresen Diet #2) (379)

TECHNICAL NOTES The patient with persistent bowel or allergic symptoms is placed on a diet consisting only of gelatin, rice rye peas raspberries grapes and tea, and is carefully observed for several days A detailed diary is also kept

CLINICAL CLUES A prompt or gradual remission on this temporary regimen points to a possible allergic basis for the disorder Likewise the absence of a change in the patient s course usually rules out such an explanation

DRUG INTOXICATIONS

Cessation of Vitamin A Therapy

TECHNICAL NOTES Large amounts of vitamin A concentrates are used in the treatment of various skin eye renal ear and gynecologic disorders and as prophylaxis against the common cold

CLINICAL CLUES The numerous diverse manifestations of hypervitaminosis A in the central nervous system skeletal system and skin will subside on this regimen (p 402) (T-1173 1174)

Cessation of Vitamin D Therapy

TECHNICAL NOTES Large amounts of this vitamin are still widely employed in the symptomatic treatment of arthritis

Clinical Clues The profound symptoms due to the hypercalcemia, the metastatic calcifications the anemia and the uremia are all potentially reversible (p 403) (T-1175 1176) Some patients with hypoparathyroidism are uniquely prone to vitamin D poisoning even on ordinary doses (T-81, 82)

Abstinence from the Opiates and Barbiturates (381) (T-1164)

Technical Notes Also see 'The Provocative Tests (p 824)

Clinical Clues A typical withdrawal syndrome ensues if addiction with physical dependence is present Addiction is now being reported from the use of the so-called tranquilizers

SECTION XVI

Provocative Tests

CARDIOVASCULAR DISORDERS

Thrombophlebitis Suspect (393)

TECHNICAL NOTES A blood pressure cuff is placed around the calf or thigh and is slowly inflated over a period of 10 to 15 seconds One should watch for a change in the patient s facial expression or a withdrawal reaction (If a question of hypersensitivity to pain arise the test should be performed on the arm Most people can briefly tolerate 250 mm of mercury)

CLINICAL CLUES Normally no pain is experienced below 180 mm of mercury Considerable pain in the 60 to 150 mm of mercury range is usually felt if thrombophlebitis is present

Carotid Sinus Syndrome Suspect (T-888 890) (see Section IX, p 778)

TECHNICAL NOTES Pressure is exerted unilaterally over the carotid bifurcation with simultaneous electrocardiographic monitoring The right side is usually more sensitive The sitting position also enhances the sensitive reaction

CLINICAL CLUES A reproduction of asystole or the patient s symptoms, or both, occurs in the carotid sinus syndrome It is cautioned that rigid clinical criteria must be adhered to since a hyperactive carotid sinus reflex may exist in normal individuals (p 293) (T-890)

Angina Pectoris (Coronary Artery Disease) Suspect (395, 402)

TECHNICAL NOTES The two-step test (Master s tolerance test) or the anoxemic test (10 per cent oxygen) may be employed One should *always* precede these with a control electrocardiogram and discontinue if symptoms are produced If available both control of the induced hypoxia by an oximeter and concomitant ballistocardiography can considerably enhance the accuracy of the anoxemia studies particularly in the preanginal period

An attempt should be made to simulate the conditions under which the angina appears clinically particularly with reference to exercise after eating Holding an ice cube in the right hand during the exercise for several minutes may also help to produce a positive test It is wise to defer such studies if the discomfort in question has been present for only one or several weeks

CLINICAL CLUES May offer valuable objective evidence of induced coronary insufficiency (myocardial ischemia) for diagnostic legal, and insurance purposes

Pulmonary Resection Tolerance Test (T-1272f)

TECHNICAL NOTES The right or left main pulmonary artery can be occluded for up to 2 hours by means of a special triple-lumen cardiac catheter with an inflatable cuff No untoward effects were observed from this method in over 100 unanesthetized patients

CLINICAL CLUES This technique allows the thoracic surgeon to anticipate the feasibility of a planned pulmonary resection along definitive physiologic lines In control individuals there is an increase in unilateral pulmonary blood flow without the changes secondary to exercise These controls demonstrate no pain or changes in the electrocardiogram the systemic arterial blood pressure the cardiac output and either oxygen saturation or consumption Marked changes in cardiopulmonary dynamics will take place if the remaining lung with its vascular bed would be unable to cope with the circulation should the contralateral lung be removed (p 450)

Evaluation of the Relationship of Esophageal Disease to Angina Pectoris (390)

TECHNICAL NOTES A Pilling balloon tied to a short Miller Abbott tube is placed 5 cm above the cardioesophageal junction and is rapidly inflated with 40 cc of air The subjective and electrocardiographic responses are both carefully noted

CLINICAL CLUES Unfortunately this is a relatively unreliable diagnostic test due to the nonspecific localization of visceral pain (Also refer to the pneumoperitoneum technique under The Therapeutic Diagnostic Tests ' p 810)

CENTRAL NERVOUS SYSTEM DISORDERS

The Migraine or Histamine Cephalgia Suspect (384, 399)

TECHNICAL NOTES Nitroglycerine in a dose of gr 1/50 is administered sublingually or histamine (0 35 mg base) is injected subcutaneously

CLINICAL CLUES Either agent may provoke migraine or a histamine cephalgia if nondiagnostic atypical features are present in a patient with headache The typical histamine cephalgia attack occurs about 15 to 50 minutes after cessation of the expected histamine headache and the ensuing latent period The induced attack can usually be promptly aborted by giving 1 ml of dihydroergotamine (DHE 45) intravenously

Hyperventilation Syndrome Suspect (392)

TECHNICAL NOTES Hyperventilation is induced preferably during the course of physical examination of the chest

CLINICAL CLUES The typical giddiness paresthesias and other symptoms are apt to ensue after only several deep breaths if this syndrome is present Hyperventilation may also help in differentiating organic and functional hyperinsulinism (T-51) In addition it has been used to induce an epileptic seizure which can be seen clinically or in the electroencephalogram

Tussive Syncope Suspect (387, 396)

TECHNICAL NOTES An attempt is made to reproduce a vigorous cough or the Valsalva maneuver under circumstances simulating those during which the

clinical attack occurred (i e , after smoking, eating, alcohol, or hyperventilation) The patient is observed for induced changes in body tone or position, consciousness, and seizures

CLINICAL CLUES Although it has been reproduced only infrequently, a positive test may be helpful in excluding epilepsy, catalepsy, and narcolepsy

Labyrinthine Sensitivity (the "Minimal Caloric Test") (385)

TECHNICAL NOTES One tests for caloric induced nystagmus and vertigo The *patient is seated with his head upright and with his eyes fixed on the* examiner s finger The finger is held laterally and slightly higher than the level of the eyes at a distance of 20 inches By means of an ordinary urethral catheter, 5 ml of cold (55° F) or very cold (35° F) water is injected into the external ear

CLINICAL CLUES Depending on the onset of the nystagmus and its duration, the labyrinthine response is designated as ' normal (onset in 15 to 30 seconds and duration of 60 to 120 seconds) sensitive (onset in less than 10 seconds, and duration of more than 120 seconds) or insensitive (onset later than 60 seconds and duration of less than 30 seconds) The anatomic localization of lesions in various part of the vestibular complex may be achieved with considerable accuracy by knowing the site of the stimulation (with reference to the position of the individual semicircular canals) along with the presence or absence of nystagmus and vertigo

DRUG INTOXICATIONS

Narcotic Addiction Suspect (403, 404)

TECHNICAL NOTES A subcutaneous injection of 15 mg of N allylnormorphine (Nalline) is administered The pupillary response to smaller doses of Nalline (3 mg) might also be diagnostic A reduction in the size of the pupil of 0 5 to 2 mm indicates that the patient is *not* an addict

CLINICAL CLUES A typical 'abstinence syndrome is promptly induced within 45 to 60 minutes and subsides during the next hour if addiction and physical dependence to opiates is present In the addict not only will the aforementioned response occur but the size of the pupil will increase by 0 5 to 2 mm There may be no change in the pupils in the individual who is an occasional user of narcotics but not an actual addict

Digitalis Intoxication Suspect (394, 401)

TECHNICAL NOTES Acetyl strophanthidin (0 3 mg diluted in 5 ml) is injected intravenously every 5 minutes until a total of no more than 1 2 mg has been given Acetylstrophanthidin should never be used without electrocardiographic control, since the signs of toxicity can occur without symptoms and may not be recognized

CLINICAL CLUES This has been referred to as a digitalis tolerance test ' Evidence of toxicity occurs within 1 to 5 minutes after the administration of 0 15 or 0 3 mg if digitalis toxicity is present but lasts only 30 minutes Further experience with the acetyl strophanthidin test has shown that while it may indicate the safety of additional digitalis administration it cannot be used to indicate the state or adequacy of previous digitalization

HYPERSENSITIVITIES

Hypersensitivity Suspect (Foods, Oral Medications, and Parenteral Drugs) (400)

TECHNICAL NOTES The patient is observed carefully for symptoms eosinophilia a rash and fever after a small amount of the offending substance is administered, preferably in a guised manner either by mouth or parenterally

In patients who are to receive a series of penicillin injections a severe allergic reaction of the anaphylactoid type might possibly be prevented by the application of the full strength procaine penicillin solution into both the conjunctival ac and a skin scratch (406)

CLINICAL CLUES Clinical or laboratory evidences of hypersensitivity often become evident The patient should ingest a suspected noxious food or medication since the offender may actually be some metabolic breakdown product that is formed in the gastrointestinal tract Probable penicillin hypersensitivity is suggested by the finding of an area of erythema that exceeds 1 cm or a more severe reaction This would suggest the use of either another form of penicillin or a completely different antibacterial agent

Food Allergy Suspect—the Provocative Diet (Andresen Diet #1) (379)

TECHNICAL NOTES Milk egg wheat potato and orange are given during a relatively symptom free period to the patient suffering from recurrent attacks of a presumed food allergy (colic diarrhea migraine vomiting etc) Other suspected noxious foods are then individually added and a careful diary is kept

CLINICAL CLUES A sudden violent exacerbation of the aforementioned symptoms suggests a factual food allergy as the basis for the patient s attacks

Wheat (Gluten) Sensitivity Suspect (T–157)

TECHNICAL NOTES The gluten fraction in wheat or rye is ingested during a temporary remission in steatorrhea

CLINICAL CLUES A prompt induction or exacerbation of the spruelike syndrome ensues if the patient is sensitive to this particular foodstuff

Skin Sensitivity (Contact) Suspect (388, 398)

TECHNICAL NOTES Patch testing is very useful but there are many potential errors in both technique and interpretation (viz improper concentrations, the closed method too short a period of observation nonspecific polyvalent sensitization and cross sensitization) Control testing should be carried out when dealing with the primary irritants Uninjured skin contiguous to the involved area is the preferred site for testing

CLINICAL CLUES Proper skin testing may be very valuable in the diagnosis and management of the occupational dermatoses Patch tests should not be overemphasized or unjustifiably exploited, however

Tobacco Sensitivity Suspect (397, 405)

TECHNICAL NOTES Vasodilation is produced by applying a wool blanket to the body and giving 1 oz of whisky to bring the digital skin temperature to 36 C The subject then smokes a cigarette in 3 minutes Changes in the skin

temperature are noted using one of several techniques Normally, the decrease is not more than 2° C for longer than 10 minutes

CLINICAL CLUES Hyperreactors exhibit excessive and prolonged decreases in skin temperatures (It should be noted that many patients with primary Raynaud s disease and arteriosclerosis obliterans are not hyperreactors)

Light Sensitivity Suspect (389) (T–1393)

TECHNICAL NOTES The skin is exposed to sunlight, ultraviolet light, or other light spectra (using colored or Corning glass color filters—#9863 for the ultraviolet spectrum, and #3389 for visible and infrared light) Only part of the skin need be exposed if marked light sensitivity is suspected Prior to testing, local tar preparations and oral medication, particularly the sulfonamides and barbiturates should be avoided

CLINICAL CLUES This test may aggravate or precipitate an acute porphyria acute solar urticaria or eczema, lupus erythematosus, pellagra, epidermolysis bullosa and xeroderma pigmentosa (pp 523 and 524)

Suspected Transfusion Incompatibility (T–1286b)

TECHNICAL NOTES A biologic cross match is performed This is done by giving small amounts of the donor blood (not exceeding 50 ml) and checking the level of free plasma hemoglobin 10 or 15 minutes later

CLINICAL CLUES A rise of the plasma hemoglobin above 10 mg per 100 ml is indicative of incompatibility This test is particularly valuable when 'subclinical sensitization may have been produced in patients who require long term transfusion therapy

Cold Sensitivity Suspect (I) (386, 389)

TECHNICAL NOTES Various techniques are employed including the cold room and the immersion of the hands in iced water

CLINICAL CLUES Helps in evaluating suspected cold 'allergy,' Raynaud s phenomenon hypertension suspects, and cryoglobulinemia The urticaria localized at the site of a 5-second ice cube application in certain patients with cancer is suggestive of an associated cryoglobulinemia (T–807) This may be an evanescent phenomenon however, particularly after the tumor is removed

Cold Hemoglobinuria Suspect (II) (The Rosenbach Test) (T–705)

TECHNICAL NOTES The serum and urine are analyzed for evidence of hemolysis following the immersion of the patient s hands or feet in iced water

CLINICAL CLUES The induction of a hemolytic episode by chilling is characteristic of syphilitic cold hemoglobinuria It is not specific for this disorder however, as it may also occur in the presence of cold agglutinins Some caution is required, inasmuch as excessive hemolysis can cause much renal damage

"Histamine Diencephalic Syndrome" Suspect (399)

TECHNICAL NOTES An intradermal injection of 0 2 mg of histamine base is given in the forearm The patient s reaction is observed in 5 10 and 15 minutes

CLINICAL CLUES A positive test is indicated by circumoral pallor, flushing of the face headache, tearing lacrimation, and a blotchy erythema over the face and strap-line of the neck

METABOLIC DISEASES

Latent Tetany Suspect

TECHNICAL NOTES Several clinical tests are employed

1 *The Chvostek sign*—not too dependable particularly in the case of children and infants
2 *The Trousseau sign*—carpal spasm after a tourniquet is applied to the upper arm
3 *The peroneal sign*—dorsiflexion and abduction of the foot on stimulation of the peroneal nerve inferior to the head of the fibula

CLINICAL CLUES The second and third signs are usually pathognomonic of tetany but occur in only 50 per cent of these cases Tetany results more often from impaired absorption of calcium than from excessive calcium excretion (since a compensatory acidosis is usually present in the latter instance)

Diabetes Mellitus Suspect (383)

TECHNICAL NOTES Glucose tolerance tests are performed before and after the administration of cortisone Cortisone acetate is given orally in 2 doses (50 mg or 62 5 mg each depending on the body weight) 8½ hours and 2 hours preceding the glucose ingestion

CLINICAL CLUES *This test may help to uncover the preclinical diabetic* in the potential group among the relatives of known diabetics It has been shown that one fourth of these nondiabetic relatives exhibit a marked loss of carbohydrate tolerance during this test

Periodic Paralysis Suspect (T-299)

TECHNICAL NOTES The patient is given one or several carbohydrate meals or peroral glucose The serum potassium and electrocardiogram are also followed Administration of insulin or epinephrine (Adrenalin) may potentiate the response

CLINICAL CLUES *These procedures all* enhance the migration of potassium from the blood into muscle and result in typical hypokalemia Attacks of paralysis are most apt to occur during the night due to the exaggerated diurnal variation in this direction at that time

Familial Hyperlipemia Suspect (T-283)

TECHNICAL NOTES A fat tolerance test is performed consisting in the ingestion of a meal containing about 90 gm of either dairy or vegetable fat The appearance of the plasma or serum is noted in the fasting and in the postprandial states *Where available determination of the blood lipid fractions and of the alpha* and beta lipoproteins should be performed periodically over a period of 30 hours

Dietary fats are normally removed from the blood within 8 hours after eating If only the blood cholesterol is determined it may be difficult to differentiate this entity from essential familial hypercholesterolemia

CLINICAL CLUES In the absence of other causes of hyperlipemia (i e renal disease myxedema diabetes mellitus), the presence of lipemic serum in the fasting state and in the 30-hour specimen is very significant Chemical hyperlipemia persisting for over 12 hours is highly suggestive particularly in the younger patients whose serum may not appear lipemic

INFECTIONS

(Also see skin tests in Section VI)

Suspected Subphrenic Abscess (T-1319)

TECHNICAL NOTES With the patient either standing or lying on the fluoroscopic table external stimulation of the phrenic nerve is performed A saline moistened electrode is used over the scalenus anticus muscle A forceful diaphragmatic descent of from 3 to 5 in is normally forthcoming

CLINICAL CLUES When a subphrenic abscess is suspected and the patient cannot take a satisfactory deep breath—as may occur in the postoperative state—the absence of any diaphragmatic contraction may help to identify inflammation below (or above) the diaphragm

Leprosy Suspect (T-636, 637)

TECHNICAL NOTES The local reaction to an intradermal injection of either 1 1000 histamine or pilocarpine is observed

CLINICAL CLUES If impairment of neural function exists in a suspected leprid, only the wheal is noted in response to the histamine, but without an erythematous halo Impairment of the normal pilocarpine-induced sweating is also observed

NEOPLASMS

Pheochromocytoma Suspect (T-62 64)

TECHNICAL NOTES Avoid the provocative tests when the blood pressure is 200 mm of mercury or more The cold pressor response is used as the control rise Regitine should be on hand if needed for a marked overshoot Abstinence from all medication for at least 24 hours (longer if taking Rauwolfia or thiocyanate) is essential for accurate testing (p 21)

CLINICAL CLUES These are valuable screening tests in the presence of labile hypertension with severe symptoms and in atypical cases of hypermetabolism False-positive or false-negative responses may be due to previous sedation or the presence of azotemia

HISTAMINE TEST

TECHNICAL NOTES *0 025 to 0 05 mg of the base is given intravenously*

CLINICAL CLUES A high percentage of false positive tests occurs in hyper reactor hypertensive patients (T-62) One can confirm the significance of a positive response by attempting to block it with Regitine prior to repeating the test

METHACHOLINE (MECHOLYL) TEST

TECHNICAL NOTES 10 mg administered subcutaneously is usually a sufficient dose This test should be avoided in patients *with concomitant asthma* or angina pectoris

CLINICAL CLUES Fewer false-positives are elicited with methacholine than with histamine The maximum response in blood pressure usually occurs in 4 to 8 minutes (T-62)

TETRAETHYLAMMONIUM TEST

TECHNICAL NOTES 100 to 300 mg of Etamon are given intravenously and the blood pressure response is noted at 1 minute intervals If very high readings are obtained they may be readily controlled by having the patient sit or stand This test is also used as a preoperative lability guide to the hypotensive results that might be anticipated with a sympathectomy it should be performed with caution however if the possibility of a pheochromocytoma exists

CLINICAL CLUES Although a high overshoot (i e exceeding the cold pressor response) may occur in pheochromocytoma a high percentage of patients with essential hypertension also exhibit a similar reaction (T–62a) Furthermore a number of false-negative reactions have also been recorded A striking hypertension alternating with hypotension following tetraethylammonium chloride (TEAC) has been observed in the presence of this tumor and is attributed to the autonomic nervous system blockade of the usual compensatory responses

Carcinoid Tumor Suspect (T–1073c)

TECHNICAL NOTES Histamine is injected intravenously (0 05 mg of the base) The blood and urine serotonins may be measured (but are performed only in a few laboratories at the present time) The intravenous injection of 5 mg of reserpine can also precipitate the clinical syndrome of metastatic carcinoid presumably due to the cellular release of serotonin (T–1072c)

CLINICAL CLUES Reproduction of the clinical syndrome along with hyper serotonemia is suggestive of a metastatic argentaffinoma

Evaluation of Hormone Dependency in Metastatic Cancer (370) (T–310 313)

TECHNICAL NOTES A 5 to 7-day control period of urinary calcium deter minations is necessary During this time, the patient is placed on a diet containing a maximum of 200 mg of calcium A provocative dose of hormone is then administered intramuscularly for 3 days consisting either of 100 mg of testosterone propionate (in prostatic cancer) or 5 to 10 mg of stilbestrol (in carcinoma of the breast) The levels of urinary calcium and the clinical response are carefully followed

The cortisone-suppression test (see under The Therapeutic Diagnostic Tests) may be preferable in patients who already are experiencing severe symptoms of their disease (p 814)

CLINICAL CLUES A positive response (indicating hormonal dependency of the tumor) is indicated in two ways (1) mobilization of calcium from the skeleton causing hypercalciuria and hypercalcemia (particularly helpful when extensive bone metastases are present) and (2) a systemic reaction characterized by malaise increase in bone pain pyrexia and lethargy (more apparent in the presence of predominately soft-tissue metastases) This test should be done with some care because a very severe systemic reaction might necessitate an emergency ovariectomy or adrenalectomy

Hodgkin's Disease Suspect (T–659)

TECHNICAL NOTES The patient should be observed for the induction of pain shortly after the ingestion of ethyl alcohol

CLINICAL CLUES Some patients with Hodgkin s disease will experience intense pain at the site of their disease after drinking alcohol It may in fact be

the first clinical evidence of the disease This response has been noted to disappear shortly after therapy is instituted

Unfortunately, this test is not pathognomonic for Hodgkin's disease since alcohol induced pain has also been observed in patients suffering from other types of neoplasms (pancreatic, thymic) (T-659c) Positive alcohol tests have also been encountered in apparently normal individuals or in the presence of such non neoplastic disorders as acute lymphangitis chronic osteomyelitis, and a fractured hip (T-659d)

Cancer of the Prostate Suspect (T-79c)

TECHNICAL NOTES Where the diagnosis of cancer of the prostate is suspected in the face of normal values for both the 'prostatic' and total serum acid phosphatase a provocative test with 50 mg of testosterone three times a week can be given

CLINICAL CLUES This course of male hormone will usually induce diagnostic elevations in the 'prostatic' acid phosphatase if a malignancy is present (p 690) (T-79c)

GASTROINTESTINAL DISORDERS

Soda Water Test for Pyloric Obstruction (391)

TECHNICAL NOTES After the abdomen is examined, the patient drinks 5 to 10 oz of soda water or enough to distend the stomach with fluid and liberated gas The gastric bulge is then observed to see whether peristalsis *is absent or* present If it occurs the test is considered 'soda water positive' Normal peristalsis is infrequently seen, even with a thin abdominal wall

CLINICAL CLUES This test is merely a modification of others that were utilized in previous years (dating back to Osler) as a means of initiating visible gastric peristalsis in instances of suspected pyloric obstruction due to peptic ulcer malignancy, and hypertrophic pyloric stenosis The test may be positive in the absence of vomiting and even in some instances where the gastric x rays were not conclusive for obstruction Unfortunately the test is also positive in many individuals with functional dyspepsia This study may be of some value in helping to define the relationship of various painful areas and masses to the stomach

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